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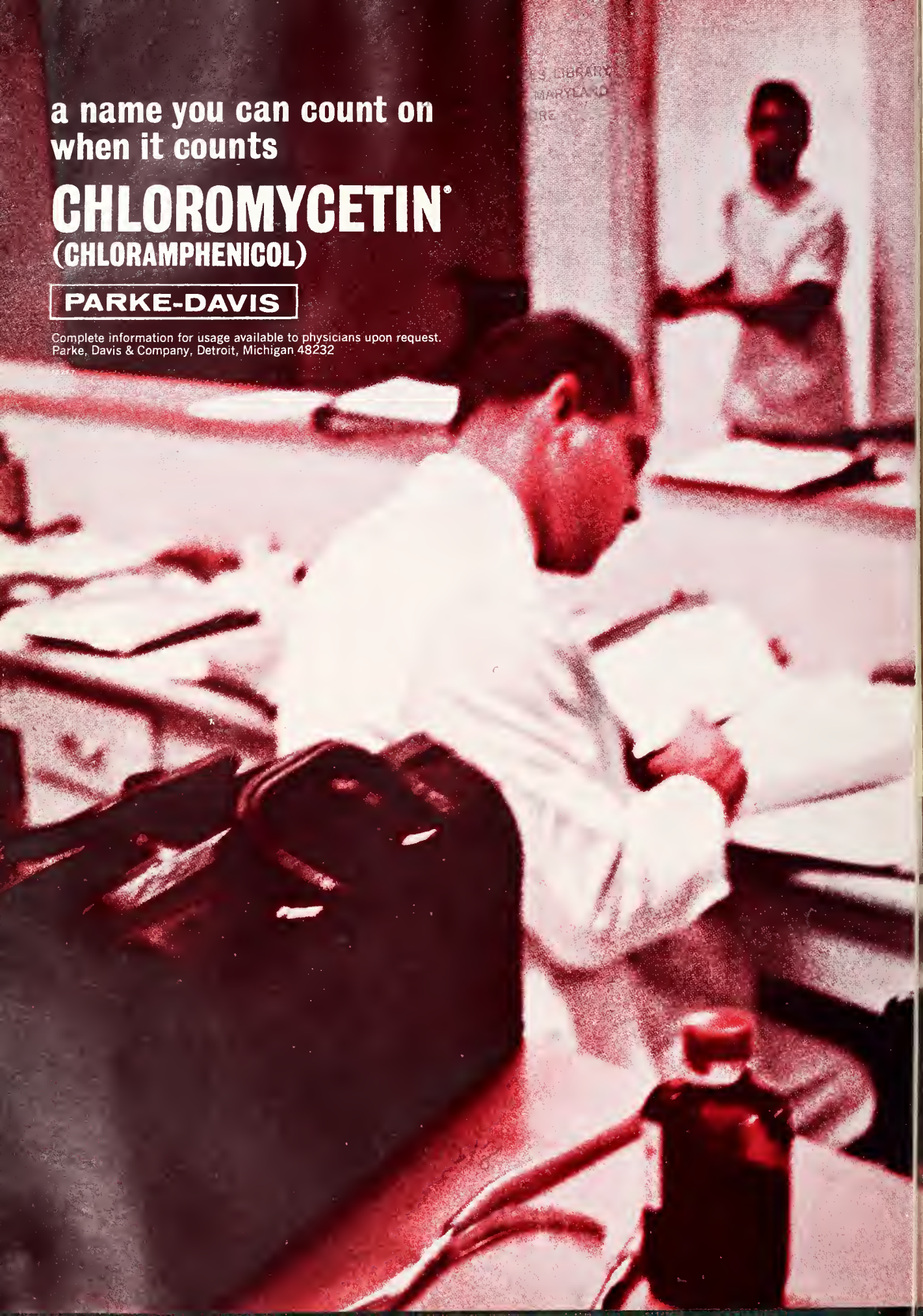
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California Medicine

Trophoblastic Tumors of the Uterus

Problems of Methotrexate Therapy

F. DEBORAH JOHNSON, M.D., EDWIN M. JACOBS, M.D., AND WILLIAM M. SILLIPHANT, M.D.,* *San Francisco*

■ *Nineteen patients with trophoblastic tumors of the uterus were evaluated at the University of California San Francisco Medical Center. Eight patients, admitted before 1956, did not receive chemotherapy; the mortality rate was 87.5 per cent. Ten of the remaining 11 patients were given intermittent, intensive Methotrexate therapy; actinomycin D and vincristine were used in treating two patients in whom resistance to Methotrexate developed. The mortality was 10 per cent. Toxicity was a prominent factor but was completely reversible when chemotherapy was stopped.*

None of the patients showed recurrent disease during follow-up evaluation eight months to five years and eight months after therapy was completed.

It is postulated that continuing chemotherapy four to six months after the chorionic gonadotropin titer becomes negative decreases recurrent disease.

THE MOST ENCOURAGING experience in the chemotherapy of cancer is the treatment of choriocarcinoma of the uterus and its related trophoblastic tumors. The outlook has changed dramatically since 1940 when Ewing[6] stated that the majority of cases of choriocarcinoma pursue a fatal course. At present, this group of tumors represents the only cancer that can be consistently cured with chemotherapy.

The rationale for using antifolic acid agents in the treatment of trophoblastic neoplasms stems from the work of several investigators. In 1948 Hertz[8] demonstrated inhibition of estrogen-induced growth in the monkey uterus when the animals were maintained on a folic acid deficient diet. The induction of therapeutic abortion in women by the administration of 4-amino-pteroylglutamic acid, a folic acid antagonist, was reported by Thiersch[20] in 1952. In 1956, Li and coworkers[13] used 4-

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amino-N^{10}-methyl-pteroylglutamic acid (Methotrexate) in the treatment of choriocarcinoma in women.

This report outlines our experience in the treatment of trophoblastic tumors in women at the Cancer Research Institute. A comparison is made between cases admitted before 1956 and those admitted after the availability of chemotherapy. Problems of toxicity to Methotrexate and of acquired resistance to this drug are discussed.

Materials and Methods

Nineteen patients with a diagnosis of trophoblastic tumor of the uterus were evaluated: eight patients, admitted to the University of California Hospitals between 1943 and 1956, were treated with surgical methods and did not receive chemotherapy; 11 patients admitted to the Clinical Unit of the Cancer Research Institute between April 1960 and April 1966 were treated with chemotherapy.

Tumors were classified according to morphologic criteria used by the Armed Forces Institute of Pathology,[7] as follows:

Hydatidiform mole. Gross examination of the specimen shows bulky quantities of characteristic vesicles. Hydatidiform moles are classified histopathologically with respect to their potential malignancy as apparently benign, potentially malignant, and apparently malignant.

Chorioadenoma destruens (invasive mole). Invasion of myometrium or its blood vessels by one or more villi associated with or following a hydatidiform mole. Metastasis may have occurred.

Choriocarcinoma. Pure malignant trophoblast made up entirely of chorionic cells without formation of villi, invading the myometrium. Tendency to metastasis is very prevalent.

In all of the eight cases treated surgically the histopathologic diagnosis was choriocarcinoma. Of the 11 cases treated with chemotherapy, six were choriocarcinoma, three were chorioadenoma destruens and two were hydatidiform mole, potentially malignant.

In this study, evaluation of the patients included a complete history, physical examination and histopathologic diagnosis. Laboratory studies included a complete blood cell count, urinalysis, determinations of blood ureau nitrogen (BUN), serum creatinine, fasting blood sugar (BS), total bilirubin, alkaline phosphatase (Bessey-Lowry units, normal range is 0.8 to 2.3), thymol turbidity, serum glutamic oxaloacetic transaminase (SGOT), and total serum protein. Bone marrow studies, chest roentgenograms, intravenous pyelograms (IVP) and chorionic gonadotropin titer (CGT) were always obtained. Electrocardiograms were obtained when indicated.

Gonadotropin levels* were determined on 24-hour urine collections. A modification of the Aschheim-Zondek test was used to measure mouse units (MU) per liter of urine. One MU, equivalent to ten international units (IU) is the amount of hormone present in 1 ml of undiluted urine which, when injected subcutaneously into immature female Swiss albino mice, shows corpora lutea after 96 hours. Determinations of less than 500 MU per liter were not made because at lower titers toxicity caused high mortality in the mice.

Administration of Methotrexate was the initial therapy in the ten patients evaluated. It was given intravenously at a daily dose of 20 to 25 mg for five consecutive days, unless there was evidence of toxicity. Subsequent courses were given in varying dosages at intervals of two to four weeks, or when toxicity subsided. Because two patients had progressive metastatic disease while receiving Methotrexate, they were given actinomycin D infusions once a week (2 mg in 250 ml of saline solution) concomitantly with daily chlorambucil (10 mg orally). One of these patients was given vincristine intravenously, 0.01 to 0.02 mg per kg of body weight once a week, because of progression of disease and pancytopenia during actinomycin D-chlorambucil therapy.

Toxicity was variable and included stomatitis, leukopenia, thrombocytopenia, anemia, dermatitis, diarrhea, hepatic dysfunction and impaired renal function. With one exception, all patients who received one full course of Methotrexate manifested stomatitis, or leukopenia of moderate degree, or both; elevation of BUN developed in two patients, and two patients showed hepatic toxicity, with elevation of total serum bilirubin and alkaline phosphatase. Therefore, it was necessary to assess the hematologic, hepatic and renal status carefully before and during treatment. Chest roentgenograms, tumor measurement and quantitative determination of chorionic gonadotropins were obtained after each course of therapy.

*The immunologic method for quantitative urinary chorionic gonadotropin titer determination developed by Wide using a hemagglutination-inhibition test and reported in IU per liter urine is considerably more accurate and less expensive but was not available at the University of California laboratories at the time of this study.[21]

Toxicity usually subsided within three to ten days after treatment was stopped. Treatment was resumed when the following criteria were met: (1) leukocyte count within normal range; (2) thrombocyte count 100,000 per cu mm; (3) BUN 20 mg per 100 ml or less; (4) total serum bilirubin and alkaline phosphatase near normal levels.

Results

Table 1 lists the pertinent data on the history, diagnosis, therapy, toxicity and current status of each patient in the series.

Eight patients were in hospital before chemotherapy was begun; seven (cases 12 to 18 in Table 1) died from disseminated choriocarcinoma within a year of antecedent pregnancy. Only one patient (No. 19) was alive without evidence of disease at the time of this report. This patient had a molar pregnancy in October 1949. A rising chorionic gonadotropin titer and persistent vaginal bleeding for six weeks prompted panhysterectomy; microscopic examination showed chorion-epithelioma without distinguishable villi invading the myometrium but confined to the uterus. This, then, represents choriocarcinoma cured by surgical intervention before metastasis occurred.

Of the 11 patients receiving chemotherapy, one (No. 11) received inadequate therapy and is excluded from evaluation; she was admitted to the hospital in a stuporous condition and died three days later from cerebral metastasis after having received only 2 mg of actinomycin D and 1 mg of vincristine intravenously. Seven of these patients were extremely ill at the time of admission; respiratory distress predominated in five and neurologic manifestations in two. The remaining four were asymptomatic but were treated because of persistently elevated gonadotropin titers following molar pregnancy. Remissions were obtained in all of the ten patients treated adequately. Nine are alive, without evidence of disease for periods of from eight months to 68 months after cessation of chemotherapy; all had negative gonadotropin titers and normal chest x-ray films. In one patient (No. 3), regression of pulmonary and pelvic metastatic lesions and a pronounced drop in the gonadotropin titer occurred after four courses of Methotrexate; two weeks later she died from a massive cerebral hemorrhage.

Reports of Cases

The case numbers in the following reports correspond with the numbering in Table 1.

CASE 1. — A 23-year-old white woman (gravida 1, para 0) expelled a hydatidiform mole in February 1957. In December 1959 she became pregnant and in March 1960 severe lower abdominal pain necessitated exploratory laparotomy; the finding was inoperable choriocarcinoma invading the uterus, bladder, and parametrial tissues. She was admitted to the Cancer Research Institute in April 1960 for chemotherapy.

Physical examination showed a well-nourished but acutely ill patient. Vital signs were normal. A harsh systolic murmur at the left sternal border and bilateral basilar rales were heard. The abdomen was distended; a recent midline surgical scar was present. The findings on neurologic examination were within normal limits.

Laboratory studies disclosed the following values: white blood cell count 14,400 per cu mm, hematocrit 38.9 per cent, BUN 7.6 mg, uric acid 5.0 mg, total serum bilirubin 3.0 mg, direct bilirubin 2.5 mg, and total serum protein 5.8 mg per 100 ml, and alkaline phosphatase 4.4 Bessey-Lowry (B-L) units. Serum electrolytes were within the normal range. The CGT was positive at 40,000 MU per liter. A x-ray film of the chest showed extensive bilateral pulmonary metastasis and an abdominal scout film showed partial paralytic ileus with ascites. The bone marrow was normal.

Methotrexate, 25 mg a day intravenously, was started on 5 April. Total serum bilirubin increased to 12.9 mg and direct bilirubin to 9.7 mg per 100 ml, the alkaline phosphatase was 7.3 B-L units. Leukocytes decreased to 800 per cu mm and platelets to 70,000 per cu mm. On 18 April the patient had a Jacksonian seizure. Physical examination showed slight blurring of the optic discs. No abnormalities were noted in a specimen of cerebrospinal fluid, and an electroencephalogram was compatible with generalized cerebral dysfunction of a nonspecific type. Dilantin and phenobarbital were begun to counteract further seizures. Because the hemoglobin level was 7.8 gm per 100 ml, transfusion of two units of whole blood was carried out. A second course of Methotrexate, 25 mg a day, was begun on 26 April and continued for four days. During this time the BUN increased to 32.5 mg per 100 ml. Cystoscopy showed a tumor invading the bladder and obstructing the ureteral orifices. An IVP showed massive right hydronephrosis and hydroureter, and a slight degree of hydronephrosis on the left. Abdominal distension

TABLE 1.—*Data on 19 Patients with Trophoblastic Disease*

Case	Age	Antecedent Pregnancy and Parity / Source of Tissue and Operation	Histopathologic Diagnosis / Extent of Disease	Chemotherapy: No. of Courses	Chemotherapy: Total Dose	Toxicity	Karnofsky Class.: Perf. Status Prior to Therapy	Karnofsky Class.: Toxicity	Current Status and Duration of Remission After Cessation of Chemotherapy
1.	23	Molar Gr I, p 0 D & C	ChorioCA, uterus Broad ligament, bladder, lungs, brain, liver CGT 40,000 MU/L	MTX — 13	1,632.5 mg	Hepatic: TSB 12.9 mg per 100 ml Renal: BUN 32.5 mg per 100 ml Stomatitis Leukopenia 300/cu mm	40	4+	11/66: Completely well, 68 mo.
2.	41	Molar Gr VII, p 5 AB 1 Hysterectomy	Chorioadenoma destruens, uterus Lungs CGT 1,000 MU/L	MTX — 11	1,400 mg	None	80		9/66: No evidence of disease, 50 mo.
3.	15	Molar Gr I, p 0 Hysterectomy Laminectomy	ChorioCA Pelvis, lungs, meninges CGT 320,000 MU/L	MTX — 4	550 mg	Incr. BUN Leukopenia	40	2+	Complete regression of pelvic mass. Chest x-ray normal. CGT neg 1/12/63 at 5,000 MU/L. Died 3/63; cerebral hemorrhage.
4.	15	Molar Gr I, p 0 D & C Thoracotomy	Chorioadenoma destruens, uterus Pelvis, lungs CGT 500,000 IU/24°	MTX — 7	650 mg	Stomatitis Alopecia	50	3+	10/66: Completely well, 41 mo. 9/17/65: Full-term live birth.
5.	19	Abortion Gr I, p 0 Hysterectomy	ChorioCA, uterus Kidneys, lungs CGT 80,000 MU/L	MTX — 9 Act D CB1348	1,050 mg 31.0 mg 10 mg/d X3 d, (total 80 mg)	Stomatitis Leukopenia Dermatitis	40	2+	9/66: Completely well, 18 mo.
6.	31	Term, still birth Gr VII, p 6 D & C	ChorioCA, uterus Lungs, liver CGT 40,000 MU/L	MTX — 5 Act D CB1348 VCR — 35	575 mg 15 mg 10 mg q.d., (total 270 mg) 34.11 mg	Stomatitis Hepatic: TSB 3.8 mg per 100 ml Leukopenia 1,800/cu mm	40	3+	11/66: Completely well, 20 mo.
7.	23	Molar Gr I, p 0 D & C uterus	Hydatidiform mole, class IV Uterus CGT 5,000 MU/L	MTX — 6	550 mg I.V.	Stomatitis	80	2+	11/66: No evidence of disease, 20 mo.
8.	28	Molar Gr II, p 1 D & C uterus	ChorioCA Lungs CGT 5,000 MU/L	MTX — 9	815 mg I.V.	Stomatitis Dermatitis Pancytopenia WBC 2,600/cu mm	60	3+	2/67: Living and well; no evidence of disease, 20 mo.
9.	20	Molar Gr I, p 0 Hysterectomy D & C	Chorioadenoma destruens Uterus CGT 10,000 MU/L	MTX — 4	360 mg I.V.	Leukopenia 3,800/cu mm Stomatitis	90	2+	11/66: No evidence of disease, 11 mo.

TABLE 1.—*Data on 19 Patients with Trophoblastic Disease (Continued)*

Case	Age	Antecedent Pregnancy and Parity / Source of Tissue and Operation	Histopathologic Diagnosis / Extent of Disease	Chemotherapy: No. of Courses	Chemotherapy: Total Dose	Toxicity	Karnofsky Class.: Perf. Status Prior to Therapy	Karnofsky Class.: Toxicity	Current Status and Duration of Remission After Cessation of Chemotherapy
10.	28	Molar Gr III, p 2 Hysterectomy D & C	Hydatidiform mole, potentially malignant Uterus CGT 200,000 MU/L	MTX — 3	240 mg I.V.	Stomatitis	90	1+	11/66: No evidence of disease, 7 mo.
11.	22	Molar Gr II, p 0 D & C Explor lap LP	ChorioCA Uterus, vagina, stomach, cerebrum, lungs CGT 160,000 MU/L	VCR — Act D	1 mg I.V. 2 mg I.V.		30		5/12/66: Died 3 days after admission. Autopsy: ChorioCA metastases to uterine wall, kidneys, liver, stomach, jejunum, lungs, & brain.
12.	29	Full-term live birth Gr I, p 1 Autopsy	ChorioCA, uterus Brain	None					Died 5/43, 4 mo. after delivery. Disseminated ChorioCA.
13.	23	Full-term live birth Gr I, p 1 Subtotal hysterectomy	ChorioCA, uterus	None					Died 8/54, 1 mo. after operation (4 mo. after delivery). Disseminated ChorioCA.
14.	33	Incomplete AB D & C	ChorioCA, uterus	None					Died 11/56, 13 mo. after abortion. Disseminated ChorioCA.
15.	24	Hydatidiform mole D & C	ChorioCA, uterus	Stilbestrol					Died 11/51, 4 mo. after D & C. Disseminated ChorioCA.
16.	22	Incomplete AB Gr I, p 0 Hysterectomy	ChorioCA, uterus	None					Died 4/50, 6 mo. after AB and hysterectomy. Disseminated ChorioCA.
17.	27	Hydatidiform mole Hysterectomy	ChorioCA, uterus	None					Died 11/51, 10 mo. after hysterectomy. Cerebral metastasis
18.	37	None Gr 0, p 0 Hysterectomy for fibromata	ChorioCA, uterus	None					Died 7/50, 4 mo. after hysterectomy. Evisceration; cerebral metastases.
19.	25	Molar Gr IV, p 2 D & C Panhysterectomy	ChorioCA, uterus CGT 280,000 MU/L	None					L & W 2/65; no evidence of disease; 17 yr. post-hysterectomy.

Abbreviations: Gr=gravida; p=para; AB=abortion; CGT=chorionic gonadotropin titer; D & C=dilatation and curettement; MTX=Methotrexate; Act=actinomycin; CB=chlorambucil; I.V.=intravenous; TSB=total serum bilirubin.

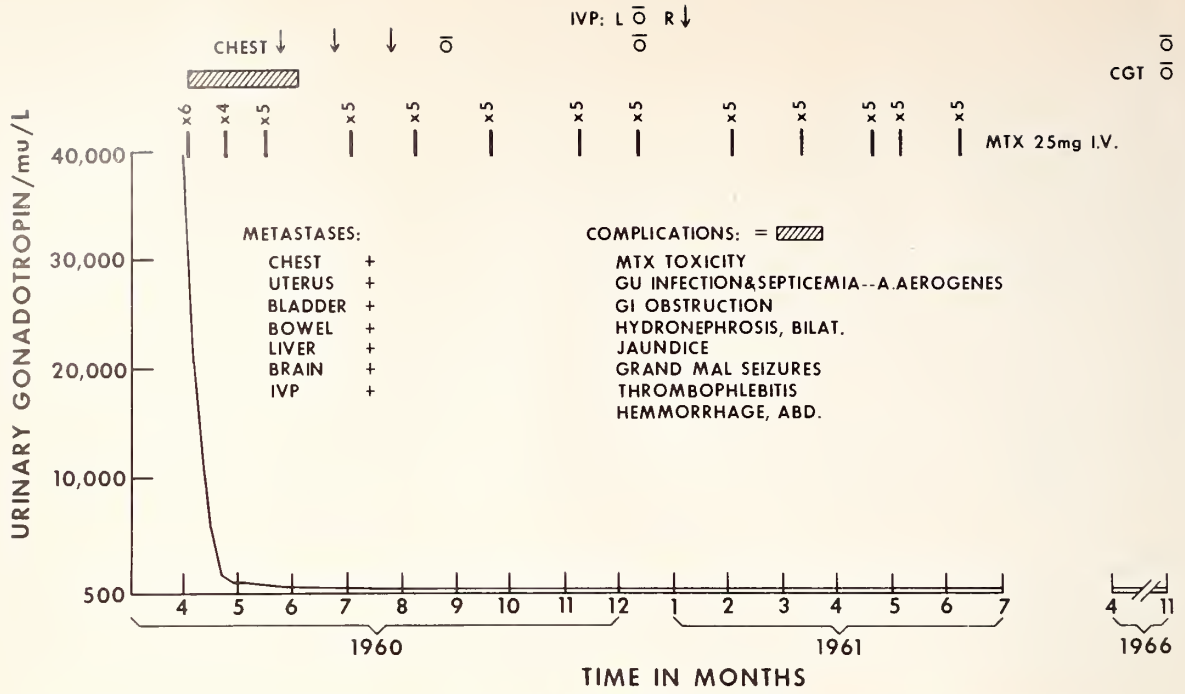


Chart 1.—Case 1: Methotrexate therapy and hormonal response in patient with metastatic choriocarcinoma.

and jaundice increased. The CGT, however, decreased to 500 MU per liter. X-ray films also showed a decrease in pulmonary nodules. Administration of Methotrexate was begun again 16 May and five consecutive daily doses of 25 mg were given. Toxicity was manifested by pancytopenia, a leukocyte count of 300 per cu mm, severe ulcerations of the buccal mucosa, generalized dermatitis and gastrointestinal bleeding with guaiac-positive stools. The patient became febrile (39.5°C, 103.1°F). Urine and blood cultures were positive for *Aerobacter aerogenes*. Penicillin, 20 million units, chloramphenicol, 4 gm intravenously, and streptomycin, 1 gm intramuscularly, were administered daily. Within four days body temperature became normal and hematologic toxicity regressed. When the patient was discharged from the hospital on 12 June 1960, hemoglobin was 12.6 gm per 100 ml, leukocytes numbered 10,200 per cu mm; total serum bilirubin was 2.7 mg per 100 ml, and CGT was negative at 500 MU per liter. She was readmitted at monthly intervals and received additional courses of Methotrexate from July 1960 through July 1961 with progressive decrease in toxic manifestations and progressive improvement in renal function. By September 1960 x-ray films of the chest showed no abnormalities. This patient received a total of 1,632.5 mg of Methotrexate. Chart 1 summarizes the courses of treatment and hormonal response. Figure 1 shows the chest roentgenograms before and after treatment. When the patient was last seen in November 1966, pelvic examination showed a left ovarian cyst without other masses. A hemogram and chest roentgenograms were within normal limits and the CGT was negative at 500 MU per liter. An IVP showed slight dilatation of the right and left renal calyces, unchanged from the previous examination (August 1961).

Comment. During therapy with Methotrexate, hematologic, hepatic and renal toxicity developed. A Jacksonian seizure was thought to be a manifestation of a cerebral metastatic lesion. Clinical improvement, a decrease in CGT, and regression of metastatic lesions in the lungs were evident with the third course of Methotrexate; hence, this therapy was continued. Because of changing pattern shown by IVP, treatment was continued for 13 months after development of a negative CGT and ten months after chest films were normal. The patient had complete remission and there was no evidence of recurrence five and a half years after treatment.

CASE 3. — A 15-year-old Negro girl had been in good health until February 1962; she reported increased girth and no menses since November 1961. On 2 February 1962 a hydatidiform mole

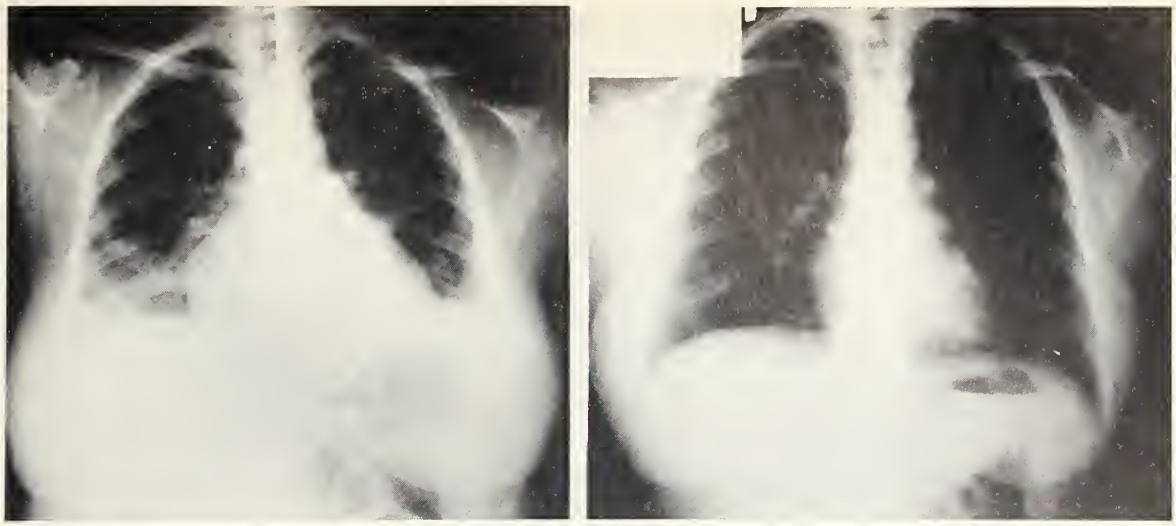


Figure 1.—Case 1: Chest roentgenograms before treatment (left) and after five courses of Methotrexate, four months later (right).

was removed by hysterotomy; endometrial curettement showed proliferative trophoblastic tissue. The gonadotropin titer was positive for the first time (1,000 MU per liter) in June 1962. The patient did not return for follow-up until September, when vaginal bleeding prompted dilatation and curettement. Because of a rising CGT and an infiltrate in the lower lobe of the left lung shown on chest films, an abdominal hysterectomy was performed (24 September). The uterus was of normal size and showed focal scarring. The postoperative course was uncomplicated; gonadotropin titers became negative (500 MP per liter) and chest films were reported to be normal. The patient did not return for follow-up until December 1962, when she had severe pain in the lumbosacral region radiating down the left leg, and difficulty in voiding had developed. She was admitted to the Cancer Research Institute on 13 December.

Physical examination showed a well-developed girl who was unable to sit or stand. There was decided tenderness over the lumbar spine and a loud bruit was heard there. In addition to a cord bladder, neurologic examination showed weakness of the lower extremities, atrophy of the left anterior tibial component and absence of left deep tendon reflexes.

Laboratory valucs for urinalysis and a hemogram were in the normal range. The BUN was 11.9 mg per 100 ml; the CGT was positive at 320,000 MU per liter. Chest films showed a small nodular density in the lower lobe of the left lung. A cisternal myelogram showed complete obstruction at the level of the twelfth thoracic and first lumbar vertebrae. A vertebral venogram confirmed the finding of an epidural obstructive lesion at the twelfth thoracic level. An abdominal scout film showed a large pelvic mass displacing the rectum and sigmoid colon, and a barium enema showed obstruction proximal to the sigmoid caused by the pelvic mass. Laminectomy and biopsy revealed a massive, friable, bleeding tumor surrounding the spinal cord. It was composed solely of fibrofatty tissue.

On 15 December Methotrexate therapy, 25 mg a day intravenously, was begun; it was discontinued after four doses because BUN increased to 27.5 mg per 100 ml. Abdominal distension and vomiting developed, secondary to partial bowel obstruction due to extrinsic pressure by the tumor. This was treated conservatively with intubation and hydration. On 3 January 1963 the BUN was 12.9 mg per 100 ml. Three additional courses of Methotrexate were given. On 11 January the chest film was normal and an IVP showed normal urinary tracts. The CGT became negative at 5,000 MU per liter and was toxic to mice at lower titers. When the patient was discharged on 9 February she had full control of bowel and bladder functions and was able to walk with crutches. On 5 March she was brought to the emergency room because of a sudden, severe headache. She was comatose when examined, with fixed, dilated pupils, and she was areflexic and hypotonic. A cisternal puncture yielded grossly bloody spinal fluid. Hypothermia was begun but her condition became progressively worse and she died within 24 hours.

Autopsy showed massive left intraventricular and left parietal cerebral hemorrhage with multiple petechial hemorrhages and cerebral edema. No tumor cells were found either within the dilated vessels or in the areas of cerebral hemorrhage. Sections from the lumbosacral segment of spinal cord, from the meninges in this area and from the epidural region of the cauda equina showed small foci of residual cytotrophoblastic tumor. A few cells appeared viable but the majority were in various stages of degeneration and calcification. The neoplasm in this area had resulted in chronic subarachnoid hemorrhage and fibrosis with associated degenerating changes of the posterior column. An area of gross induration (3 cu mm) was found in the lower lobe of the left lung. Histologically, a few small clumps of cytotrophoblastic cells and rare syncytial trophoblastic giant cells were found. More prevalent, however, were hyalinized tumor clumps with focal calcification in which "ghost forms" of once viable cells were seen. No intrinsic or extrinsic mass was found in the rectosigmoid or pelvic area.

Comment. This case demonstrates the importance of systematic follow-up in cases of hydatidiform mole. Gonadotropin titer should be determined monthly for at least six months. Chemotherapy should be initiated if the titer remains elevated for six weeks or becomes positive during the follow-up period. It is apparent that although this patient responded to Methotrexate with a dramatic decrease in the gonadotropin titer and with resolution of pulmonary, pelvic and meningeal metastatic lesions, her death was due to central nervous system complications.

CASE 5. — A 19-year-old white girl was admitted to the Cancer Research Institute 19 September 1963 because of lower abdominal pain and a positive CGT (40,000 MU per liter). Her last menses had been in May 1963. Physical examination showed an acutely ill patient who was

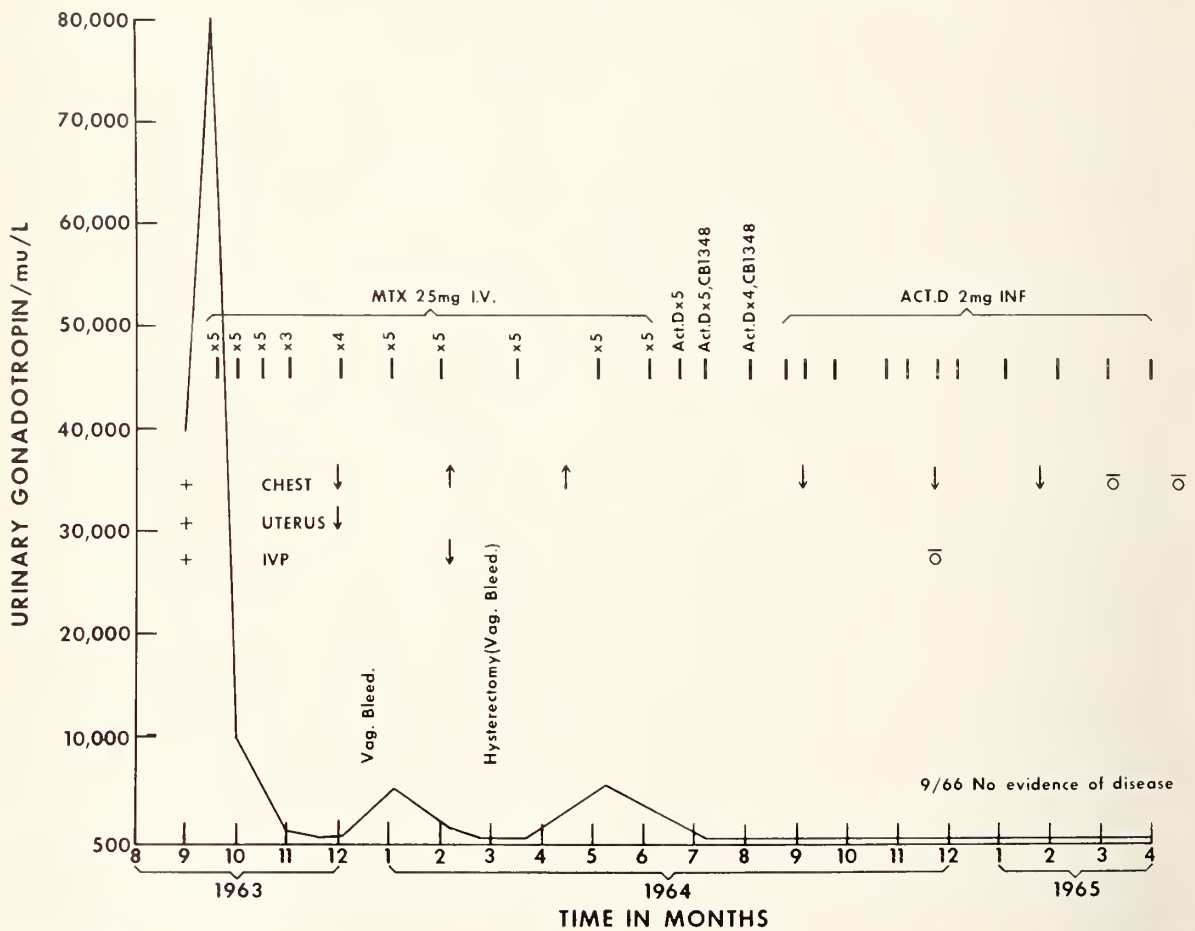


Chart 2.—Case 5: Therapy (Methotrexate followed by actinomycin D) and hormonal response in patient with metastatic choriocarcinoma.

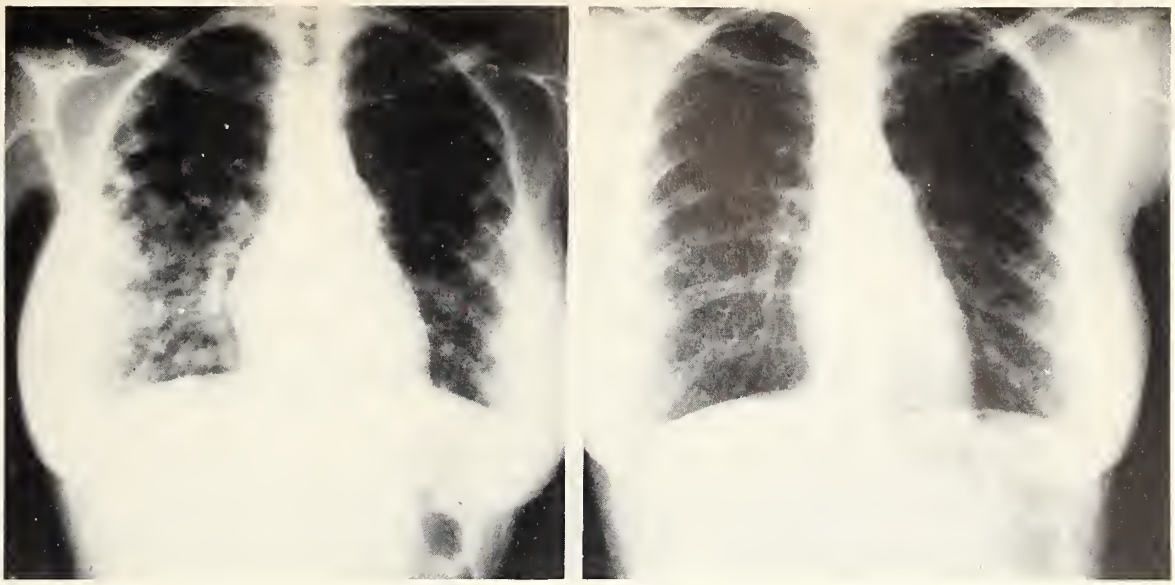


Figure 2.—Case 5: Chest roentgenograms before treatment (left) and after treatment with Methotrexate and sequential actinomycin D 20 months later (right).

severely dyspneic at rest. A firm, tender pelvic mass extended to the level of the umbilicus. Leukocytes numbered 10,900 per cu mm. The hematocrit was 33 per cent. Values for urinalysis, liver function and electrolytes were within normal limits. The BUN was 10.5 mg per 100 ml. Bone marrow was normal. X-ray films of the chest showed extensive bilateral pulmonary metastatic disease. A large pelvic mass producing partial obstruction to the lower urinary tracts with dilatation of the collecting structures and ureters was evident from an IVP. A diagnosis of choriocarcinoma was made on the basis of the clinical features and the presence of a positive gonadotropin titer.

Methotrexate therapy was begun 25 September; four courses were given at bi-weekly intervals. Toxicity included moderate stomatitis and leukopenia (4,700 per cu mm). On 27 November the CGT was negative. The pulmonary nodules had decreased and the uterus was about half its original size. Five-day courses of Methotrexate therapy were continued monthly until February 1964, when massive vaginal bleeding necessitated hysterectomy. Histopathologic examination showed well-circumscribed focal areas of necrosis throughout the uterus. A second IVP showed decreased obstruction of the right ureter and an infiltrating lesion of the left kidney. Additional courses of Methotrexate were given in March and May. In May, an x-ray film of the chest showed new parenchymal nodules in the left mid-lung, and the CGT was positive at 5,000 MU per liter. Because of progression of disease, actinomycin D (500 gamma intravenously) was begun 1 June and given for five consecutive days. Nausea, vomiting, aphthous stomatitis and leukopenia (3,200 per cu mm) developed. Chlorambucil, 10 mg orally per day, was given from 8 June to 11 June, followed by six consecutive doses of actinomycin D. On 30 June a film of the chest showed slight regression of the metastatic disease; the CGT was negative at 500 MU per liter. The patient's clinical course and treatment are shown in Chart 2. Monthly actinomycin D infusions, 2 mg in 250 ml of saline solution were given in the outpatient clinic from August 1964 through April 1965. An IVP in October 1964 showed no evidence of obstruction and both kidneys appeared normal. An x-ray film of the chest was reported as normal in April 1965 (Figure 2). When last seen in September 1966 the patient was in good health with no evidence of recurrent disease.

Comment. This patient showed an initial response to Methotrexate with a decrease in metastatic pulmonary disease and a fall in the CGT. After nine courses (total dose, 1,050 mg), the disease became refractory to Methotrexate; the CGT increased and new parenchymal nodules developed. Complete remission was obtained with actinomycin D and the patient remained well, without evidence of disease, for 20 months of observation after completion of chemotherapy.

CASE 6.—A 31-year-old white woman (gravida

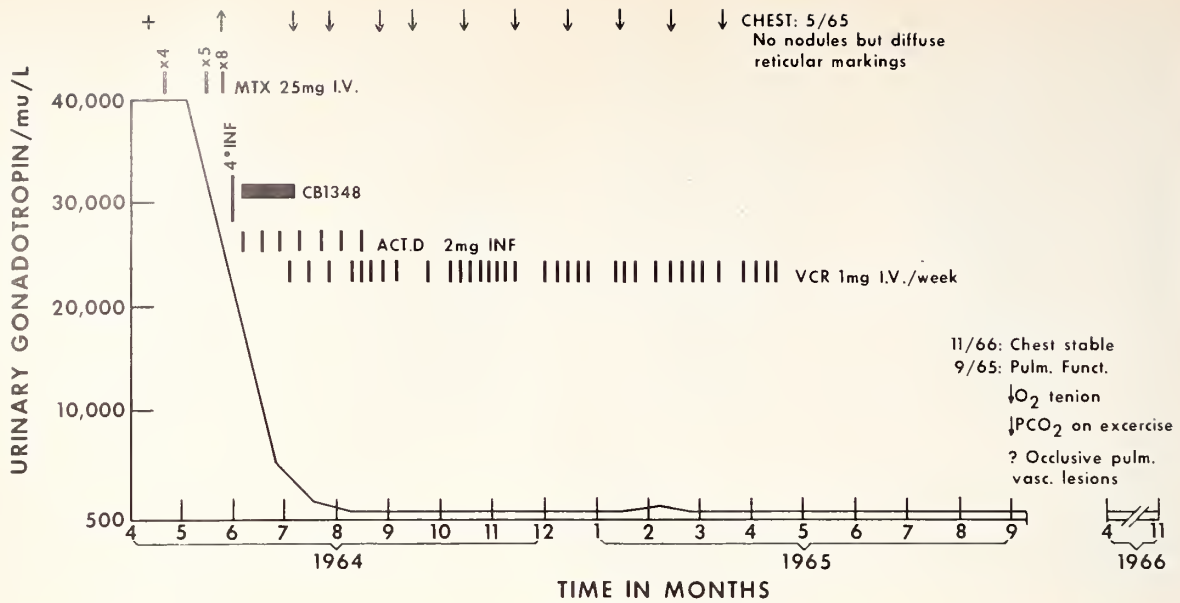


Chart 3.—Case 6: Therapy and hormonal response in patient with metastatic choriocarcinoma, resistant to Methotrexate; partial remission was evident after actinomycin D and complete remission after vincristine therapy.

7, para 6) was delivered of a full-term, stillborn infant on 3 March 1964. Vaginal bleeding, cough, hemoptysis and chest pain developed three weeks later. On 20 April dilatation and curettage showed retained products of conception. X-ray films of the chest showed multiple, nodular densities. The patient was transferred to the Cancer Research Institute on 25 April.

On physical examination, the patient was acutely ill, dyspneic and had violent hemoptysis. Scattered rhonchi were heard throughout the lungs. The liver was palpable 3 cm below the right costal margin. Abdominal fullness was noted and a globoid pelvic mass was palpable above the symphysis. There was no cyanosis or clubbing.

A hemogram was within normal limits. Urinalysis showed numerous red blood cells and positive acetone. BUN was 8 mg per 100 ml. The CGT was positive at 1,000 MU per liter. Review of the sections from the curettage disclosed clumps of pleomorphic syncytial cells compatible with choriocarcinoma of the uterus.

Methotrexate therapy was begun 26 April. After two five-day courses, the CGT was positive at 40,000 MU per liter. Eight additional consecutive doses of Methotrexate, 25 mg each, were given intravenously. On 1 June Methotrexate was given again for three additional daily doses, followed by infusion of 50 mg in a four-hour period. Serum bilirubin increased to 3.8 mg per 100 ml and alkaline phosphatase to 5.4 B-L units. The patient received a total dose of 575 mg of Methotrexate, with no regression of the pulmonary lesions. On 5 June actinomycin D, 2 mg in a 250 ml was given by infusion concomitantly with chlorambucil, 10 mg orally per day. Stomal ulcers developed and a packed cell volume of 28 per cent was noted.

Three additional courses of actinomycin D were given at weekly intervals. Chlorambucil was discontinued because of pancytopenia and an inadequate response. On 2 July vincristine, 0.6 mg (0.01 mg per kg of body weight) was given intravenously, and the drug then was given weekly in increasing doses. On 18 July leukocytes numbered 1,800 per cu mm and platelets 65,000 per cu mm. The patient had received actinomycin D, 13 mg; chlorambucil, 270 mg; vincristine, 2.5 mg; and Methotrexate (from the previous treatment) 575 mg.

Pelvic examination showed an enlarged, bulky uterus (consistent with about 12 weeks of gestation). A slight decrease in pulmonary nodules was noted roentgenographically. The CGT was positive at 1,000 MU per liter. The patient was discharged from the hospital without medications because of leukopenia. She received additional courses of actinomycin D (2 mg infusions) and vincristine (1.0 mg intravenously) at weekly intervals throughout August. Tingling of the hands and feet developed in September. At that time the uterus was near normal size. Vincristine (1.0 mg intravenously) was given at weekly intervals through



Figure 3.—Case 6: Chest roentgenograms before treatment (left); after disease had progressed, following Methotrexate therapy (center); and regression of metastases after treatment with actinomycin D and vincristine one year later (right).

April 1965. The leukocyte count varied between 1,800 and 4,500 per cu mm, and the pulmonary lesions continued to decrease. In April 1965 the titer was negative at 500 MU per liter. Chart 3 shows the courses of treatment and hormonal response. The changes in chest roentgenograms are shown in Figure 3.

Pulmonary function studies in September 1965 showed ventilatory measurements and diffusing capacities within normal limits, with slight reduction of oxygen tension. A persistent, low arterial PCO_2 on exercise was abnormal, and consistent with occlusive pulmonary vascular disease. The chest roentgenograms showed no change from February 1965 to the time the patient was last seen, in November 1966. She was then completely well. The findings of laboratory studies were within normal limits.

Comment. This patient's course illustrates primary resistance to Methotrexate with no hematologic toxicity but with moderate hepatic toxicity after massive intravenous doses. Her response to combined actinomycin D-chlorambucil was minimal, and, after one month, she was treated with vincristine instead because of pancytopenia. Complete remission occurred while the patient was receiving vincristine and when last observed, 20 months after completion of chemotherapy, she was without evidence of disease.

Discussion

The incidence of hydatidiform mole is about one in two thousand pregnancies among the occidental population, while uterine choriocarcinoma occurs in 1 in 13,850 pregnancies.[16] The tenfold greater incidence among orientals has been attributed to poor nutrition, to chronic illness such as tuberculosis and to multiparity in the older age group.[4] Over 50 per cent of choriocarcinomas are preceded by a hydatidiform mole; about 25 per cent follow abortion, 2 per cent to 3 per cent follow ectopic pregnancy, and term pregnancy is the antecedent of choriocarcinoma in 15 to 22 per cent of cases.[1,5]

The variable course of trophoblastic disease with its indeterminate frequency of spontaneous remission makes appraisal of therapeutic results difficult. Spontaneous cure occurs in 5 to 15 per cent of cases, and has been attributed to the intrinsic tendency of the trophoblast to involute, as in normal pregnancy.[3]

While the total number of patients in this series is too small to draw any concrete conclusions regarding the efficacy of specific chemotherapy regimens, it is apparent that mortality was reduced with chemotherapy. The rate was 10 per cent in the chemotherapy group, against 87.5 per cent in the group treated by surgical operation alone without chemotherapy.

Several larger series have shown that with intermittent, intensive Methotrexate therapy significant clinical remission can be obtained in 50 to 75 per cent of cases.[9,10,14] Drug resistance develops in about half the patients in whom Methotrexate therapy is at first effective. In such cases, sequential use of actinomycin D is recommended.[17,18] Other agents that have proved effective include 6-diazo-5-oxo-l-norleucine (DON, a glutamine antagonist), nitrogen mustard and chlorambucil (alkylating agents), Purinethol (a purine antagonist), actinomycin D (an antibiotic),[15] and the plant alkaloids, vincristine and vinblastine.[11] We used vincristine in combination with actinomycin D in treating one patient who had primary resistance to Methotrexate and then had pancytopenia after sequential actinomycin D-chlorambucil therapy. Vincristine has been reported to have less marrow

toxicity than vinblastine, but without careful titration it can produce decided neuromuscular toxicity, manifested by constipation, paresthesia and loss of deep tendon reflexes progressing to paraplegia.[19]

The classic treatment of patients with trophoblastic disease confined to the uterus has been prompt hysterectomy. The consistently favorable results obtained with chemotherapy alone justify this form of treatment, thus preserving the childbearing function in nulliparous women.[12] Indeed, patients who had not had hysterectomy responded better to chemotherapy than those who had.[2] This is in agreement with our experience with some patients in the present series; the one death reported was that of a patient who had had hysterectomy because of a rising chorionic gonadotropin titer following a molar pregnancy. Two other patients had had hysterectomy because of intractable uterine hemorrhage.

Emphasis should be placed on the importance of early treatment. Hertz[10] found that the shorter the duration of the disease before chemotherapy, the greater was the probability of complete remission. If treatment is delayed beyond four to six months after symptoms develop, the prognosis is poor. The deaths in our patients occurred when there had been symptoms of disease seven months (No. 3) and nine months (No. 11) before chemotherapy. The remaining nine patients, all of whom are living and well, were treated four to six months after development of symptoms or evidence of hormonal abnormality.

The patient's urinary excretion of chorionic gonadotropin, as indicated quantitatively by titer, has provided a reliable index of activity of disease as well as a guide to further therapy. However, in several of our patients with pulmonary and renal involvement, the titer became negative several months before complete regression of parenchymal involvement was manifest. Therefore, although the titer is essential in determining activity of disease, it may not always be a sensitive gauge of presence of disease, and frequent radiologic examinations are mandatory in evaluating pulmonary and renal metastasis. In some of our patients, because of changing parenchymal lesions, treatment was continued for six to fourteen months after the titer became negative. We believe that continuation of therapy four to six months after all evidence of disease is absent (as measured by clinical, hormonal and radiologic methods) is of paramount importance. It may be possible to increase the cure rate significantly by early and adequate treatment, by consecutive use of drugs if indicated by suboptimal response to Methotrexate, and by continuation of effective chemotherapy four to six months after clinical evidence of complete remission.

Conclusions

Intermittent, intensive Methotrexate therapy is the treatment of choice in trophoblastic disease in women, whether or not it is confined to the uterus. Patients must be watched carefully for hematologic, hepatic, renal and neurologic dysfunction during therapy because toxicity occurs easily. In most cases it is completely reversible if therapy is discontinued at the first signs of toxicity. Actinomycin D and vincristine are useful agents in treating patients who do not respond to Methotrexate.

The chorionic gonadotropin titer is an essential index of activity of disease and of therapeutic response, but it should be used with appropriate roentgenographic studies to determine presence of disease. Judicious and sequential use of drugs and continuation of chemotherapy four to six months after the gonadotropin titer becomes negative assure a higher cure rate and a lower rate of relapse.

Generic and Trade Names of Drugs

4-amino-N^{10}-methylpteroylglutamic acid—*Methotrexate.*
Vincristine—*Oncovin.*
Actinomycin D—*Cosmegen.*
Chloramphenicol—*Chloromycetin.*
Chlorambucil—*Leukeran.*

REFERENCES

1. Acosta-Sison, H.: Statistical study of chorion epithelioma in the Philippine General Hospital, Am. J. Obst. & Gynec., 58:125-132, July 1949.

2. Bagshaw, K. D.: Trophoblastic tumors: Chemotherapy and developments, Brit. Med. J., 2:1303-1307, 23 Nov. 1963.

3. Brewer, J. I., Rinehart, J. J., and Dunbar, R. W.: Choriocarcinoma. A report of five or more years' survival from the Albert Mathiew chorion-epithelioma registry, Am. J. Obst. & Gynec., 81:574-583, Mar. 1961.

4. Buxton, C. L.: Management of patients with hydatidiform mole, Ann. N.Y. Acad. Sci., 80:121-124, Aug. 1959.

5. Chan, D. P. C.: Chorion epithelioma: A study of 41 cases, Brit. Med. J., 2:953-957, 13 Oct. 1962.

6. Ewing, J.: Neoplastic Disease. A Treatise on Tumors, 4th Ed., W. B. Saunders, Philadelphia, 1940, Chap. 28, pp. 625-640.

7. Hertig, A. T., and Mansell, H.: Tumors of the Female Sex Organs. Part 1. Hydatidiform Mole and Choriocarcinoma, Atlas of Tumor Pathology, Armed Forces Institute of Pathology, Washington, D.C., 1956, Section IX, Fascicle 33, pp. 7-15.

8. Hertz, R.: Dietary impairment of estrogen response in immature monkey, Proc. Soc. Exper. Biol. & Med., 67: 113-115, Jan. 1948.

9. Hertz, R., Bergenstal, D. M., Lipsett, M. B., et al.: Chemotherapy of choriocarcinoma and related trophoblastic tumors in women, JAMA, 168:845-854, 18 Oct. 1958.

10. Hertz, R., Lewis, J., Jr., and Lipsett, M. B.: Five years' experience with the chemotherapy of metastatic choriocarcinoma and related trophoblastic tumors in women, Am. J. Obst. & Gynec., 82:631-640, Sept. 1961.

11. Hertz, R., Lipsett, M. B., and Moy, J. M.: Effect of vincaleukoblastine on metastatic choriocarcinoma and related trophoblastic tumors in women, Cancer Research, 20:1050-1053, Aug. 1960.

12. Hertz, R., Ross, G. T., and Lipsett, M. B.: Primary chemotherapy of nonmetastatic trophoblastic disease in women, Am. J. Obst. & Gynec., 86:808-814, July 1963.

13. Li, M. C., Hertz, R., and Spencer, D. B.: Effect of Methotrexate therapy upon choriocarcinoma and chorioadenoma, Proc. Soc. Exper. Biol. & Med., 93:361-366, Nov. 1956.

14. Li, M. C., Hertz, R., and Bergenstal, D. M.: Therapy of choriocarcinoma and related trophoblastic tumors with folic acid and purine antagonists, New Eng. J. Med., 259:66-74, 10 July 1958.

15. Li, M. C.: Management of choriocarcinoma and related tumors of uterus and testis, Med. Clin. N. Amer., 45:661-676, May 1961.

16. Park, W. W., and Lees, J. C.: Choriocarcinoma: A general review with analysis of 516 cases, Arch. Path., 49:73-104, Jan. 1950; and 205-241, Feb. 1950.

17. Ross, G. T., Stolbach, L. L., and Hertz, R.: Actinomycin D in the treatment of Methotrexate resistant trophoblastic disease in women, Cancer Research, 22:1015-1017, Sept. 1962.

18. Ross, G. T., Goldstein, D. P., Hertz, R., et al.: Sequential use of Methotrexate and actinomycin D in the treatment of metastatic choriocarcinoma and related trophoblastic diseases in women, Am. J. Obst. & Gynec., 93: 223-229, Sept. 1965.

19. Svaboda, G.: The current status of research on the alkaloids of vinca rosea linn (canthoranthus rosea G. Don) *In* Antitumoral Effects of Vinca Rosea Alkaloids, Proc. First Symposium European Cancer Chemotherapy Group, June 1965, Internat. Congress Series 106, Excerpta Medica Found., Apr. 1966, pp. 9-28.

20. Thiersch, J. B.: Therapeutic abortion with a folic acid antagonist, 4-aminopteroyl glutamic acid (4-amino P.G.A.) administered by the oral route, Am. J. Obst. & Gynec., 63:1298-1304, June 1952.

21. Wide, L.: An immunological method for the assay of human chorionic gonadotropin, Acta Endocrin., 41: Suppl. 70, 1962.



Leukemia in Animals and Man

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■ *General comparative aspects of leukemia were reviewed. Leukemia in adult cattle occurs frequently within certain multiple case herds. Cattle in these herds often have persistent lymphocytosis and increased numbers of atypical lymphocytes in blood. Attempts are being made to demonstrate the frequency in which this is a "pre-leukemic" or "perileukemic" condition.*

With the recognition of viral causative agent(s) in chickens, laboratory rodents and cats, there is increased interest in the leukemia of dogs, cattle and other animals, for the disease in these animals may serve as valuable models in the study and isolation of human leukemogenic agents.

Epidemiologic and clinicopathologic aspects of animal leukemias share comparative similarities with themselves and with lymphoreticular neoplasms of man. Causative factor(s) probably act on the host, regardless of species, in a similar fashion. It is not likely, but neither improbable, that leukemia in domesticated animals and leukemia in man share common causal relationships.

LEUKEMIA WAS FIRST DESCRIBED in man as a separate entity more than 120 years ago.[11] During the next five decades, the disease was recognized in horses, pigs, cats, cattle, mice, chickens and a variety of wild animals.[15] Now most forms of leukemia reported in human beings have been reported in animals also (Table 1).

In the broad sense, the term *leukemia* is used whether the neoplasm is in the blood phase or in solid tissues or both. It is a term that is well entrenched, but with attempts to classify the syndrome in the various animal species and man, one finds that the nomenclature becomes confusing. Although in man lymphocytic leukemia and granulocytic leukemia are of approximately equal frequency, in animals the former is much more common. The malignant lymphoreticular cells in animals usually form solid foci in the various organs and tissues, and there is not generally a true leukemic phase. It is for this reason that the terms *lymphosarcoma* and *malignant lymphoma* are used in veterinary literature in preference to *lymphatic leukemia*. In most continental European countries, the animal leukemia complex is grouped together

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TABLE 1.—*Leukemia Complex in Domestic Animals*

	Cell of Origin	Neoplastic Condition: Blood Phase	Neoplastic Condition: Blood and Tissue Phase	Neoplastic Condition: Tissue Phase	Spontaneous Frequency
1.	Undifferentiated		Stem Cell Leukemia		Rare—Most Species
2.	Granulocyte		Granulocytic Leukemia		Uncommon With Exception of Cats and Pigs
3.	Erythrocyte		Erythroleukemia		Rare With Possible Exception of Cats
		Lymphocytic Leukemia			Relatively Uncommon
4.	Lymphocyte			Lymphosarcoma	Most Common Form of Leukemia In Cattle, Dogs, Cats, Horses, Pigs, Goats, Sheep, Chickens, Laboratory Mice, and Rats
		Monocytic Leukemia			Rare—Most Species
5.	Reticulum Cell			Reticulum-Cell	Less Common Than Lymphosarcoma But Found In All Species
		Plasmacytic Leukemia		Multiple Myeloma	Rare—All Species
6.	Plasma Cell				Rare—All Species
		Mast Cell Leukemia			Rare—All Species
7.	Tissue Mast Cell			Mastocytoma	Common In Dogs, Rare In Other Species
8.	Miscellaneous, Mixture, or Unclassified				Found In All Species

and referred to as leukosis, as in the nomenclature used for avian leukosis in this country.

In 1908, Ellerman and Bang provided the first demonstration of viral leukemo-genesis by inducing leukemia in chickens with cell-free filtrates.[14] Proof of the viral causation of leukemia in animals eluded investigators, however, until Gross[17] demonstrated in 1951 that murine leukemia could be transmitted with cell-free filtrates. Since then, Jarrett[21] and Rickerd[29] and we[23] have isolated feline leukemia viruses; and recently leukemia has been transmitted in newborn puppies with cellular material.[24] It has been suspected for many years that bovine leukemia is also caused by virus because of its epidemiologic pattern, particularly its high incidence in certain herds.

Avian leukemia and murine leukemia are convenient models for investigation of the phenomena of viral induction of the leukemic processes. Leukemia in these laboratory animals has provided causative viruses in quantity suitable for study of the nature of these agents and the interrelationship and interactions with the hosts. With increased interest in the relationships of viruses to leukemia, considerable attention has not only been drawn to avian and murine leukemia, but to other animal leukemia as well. The various kinds of leukemia of dogs, cats and cattle can provide information which will perhaps bear more directly on the understanding of the epidemiologic and etiologic features of the disease in man.

Recognizing the likelihood that leukemia in man is also caused by a virus, the Congress of the United States provided a special appropriation to the National Cancer Institute for an intensified program of research in this field.[3] One goal of the Special National Leukemia Program is the isolation of agents that cause leukemia in man and domesticated animals and the development of an effective means of control.

It is the purpose of the remainder of this discussion to compare, in some aspects, leukemia in animals with leukemia in man and also to give a more detailed description of bovine leukemia.

Epidemiologic Aspects

Epidemiologic features of human leukemia are well documented, but normal demographic data is difficult or impossible to obtain for most animal cancer studies. Nevertheless, considerable information about the epidemiologic aspects of bovine leukemia is available in the literature. As early as 1916, in northern Europe the disease had been reported to spread from one herd to another and become endemic. It is now a major cause of death in some cattle herds in most major dairy producing

TABLE 2.—*Per Cent of Lymphocytosis in Lymphosarcoma Affected and Herds with No History of Lymphosarcoma*

No. of Herds Sampled	*Herd Classification*	*Location*	*No. of Samples*	*No. of Samples with Lymphocytosis*	*Per Cent of Samples with Lymphocytosis*
79	No History of Lymphosarcoma	Jersey Channel Island	434	2	0.5
7	No History of Lymphosarcoma	California	3,605	40	1.1
9	Lymphosarcoma Affected	California	3,211	357	11.1

countries.[32] Some reports indicate that dairy cattle have a higher occurrence of leukemia than do cattle of beef breeds and there is good evidence that the incidence is lower in herds of 50 than it is in herds of 200 cattle.[8] These observations have led to the suggestion that dairy cattle in large herds are more frequently exposed to leukemogenic factor(s) than are cattle in small herds. Beef cattle, on the other hand, are less likely to be exposed because of differences in husbandry practices.[33] Some cattle in endemic multiple case (MC) herds often have blood dyscrasia in the form of persistent lymphocytosis (PL) and presence of atypical lymphocytes in peripheral blood smears that may persist for months or years before development of lymphosarcoma (Table 2). In California studies it was noted that each year in MC herds, lymphosarcoma developed in approximately 5 per cent of PL cattle over five years of age. Pre-leukemic changes have also been recognized to a limited degree in human leukemia studies,[6] but no long-term hematology studies in humans have been conducted to show whether the disease in man parallels the situation in cattle.

Overall leukemia rates increase with increasing age in California cattle, up to eight years of age. Although the general age incidence histogram indicates a single peak between seven and eight years of age, a comparative distribution between herds with a single and multiple case pattern suggests that a bimodal age distribution prevails in single case herds (Chart 1). It is of considerable interest that cattle younger than two years are rarely affected with leukemia in MC herds, although the reasons for this difference are not known. In man, there is also a bimodal age incidence, but whether the causal factor(s) in children differ from those in adults as they may in cattle is a question yet to be answered.

Clinico-pathologic Changes

On the basis of detailed clinical and pathologic

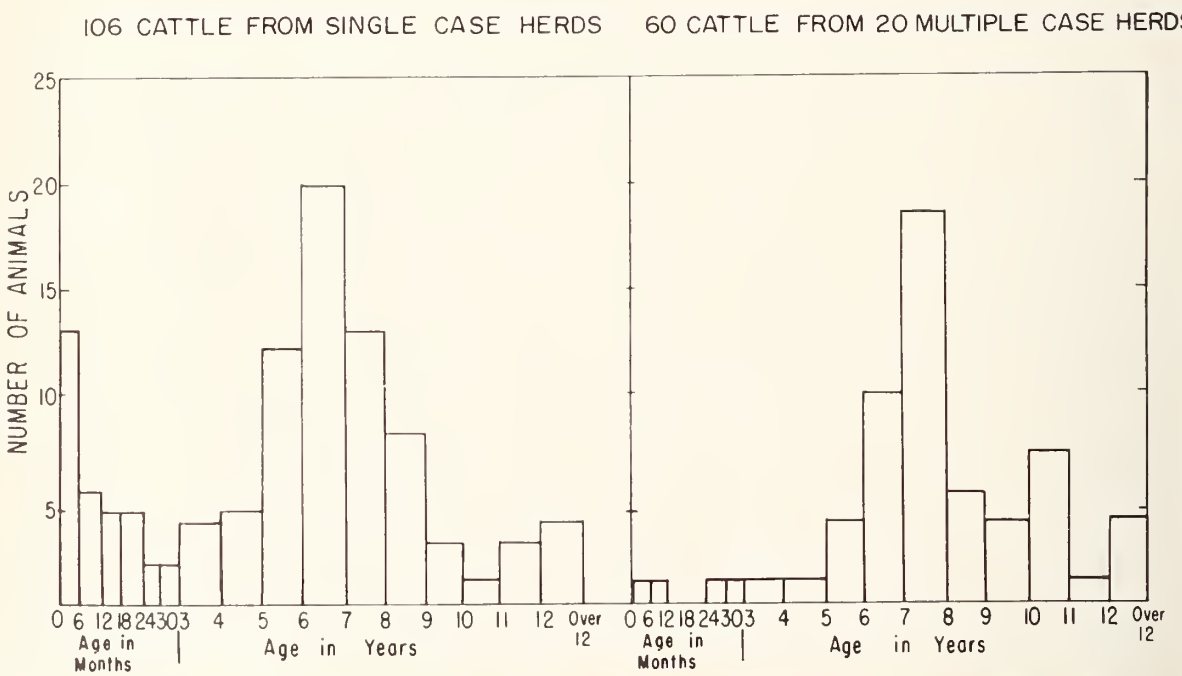


Chart 1.—Age distribution of 166 cattle with lymphosarcoma divided by single or multiple case herds.

examination of lymphosarcoma in cattle four types of bovine lymphosarcoma are recognized. The criteria for separation into four types are primarily age of animal and distribution of lesions. One type, the *calf form* is seen in calves from birth to around six months of age.[35] Approximately 80 per cent of the calves with lymphosarcoma are of the dairy breeds. All calves have generalized neoplastic lymphadenopathy; other organs consistently affected are bone marrow, liver, spleen and kidney. The second type, the *adolescent thymic form,* occurs in California most frequently in beef cattle of the Hereford breed between six and thirty months of age.[13] The main pathologic changes are extensive infiltrations of the thymus, and frequent involvement of the bone marrow. Regional lymph nodes are usually affected but generalized lymphadenopathy is rare. The third type, the *adult form,* is observed most frequently in dairy cattle, two years of age and older.[34] The most characteristic gross pathologic features are variable and widespread lymphadenopathy, and frequent involvement of the abomasum, heart, intestine and spinal epidural space. The bone marrow and thymus are rarely involved. A fourth type, the *skin form,* rarely described in the United States, is characterized by infiltrations in the dermis with or without involvement of the visceral organs.[5]

It is interesting that lymphosarcoma in young individuals is often quite similar, regardless of species, with generalized lymph node involvement and infiltrations of the spleen, liver, kidneys and bone marrow. In adolescence, the thymus and regional and mediastinal lymph nodes may be the only tissue involved. In adults, clinical signs vary according to tissue involvement which may be widespread with no general consistency to pattern.

Etiologic Aspects

It was not until syngenetic strains of chickens and mice were developed that research workers could attain consistent and repeatable experimental transmissions. Although there are no syngenetic strains of cattle, the disease has been reported to have a higher incidence in certain cow families, which could mean that genetic aspects are also important in understanding and evaluating susceptibility to the bovine disease.[9] It seems quite clear, however, from available literature, and from studies carried out at the University of California at Davis, that a simple Mendelian pattern of inheritance is not involved. This probably indicates implication of multiple factors. While chromosome abnormalities have been shown to be associated with the disease, they are variable and no consistent chromosomal aberration has been found.[20] The demonstration and measurement of the role of inheritance in bovine leukemia will probably have to come from selection experiments. These might be carried out in large experimental herds, or through careful design and extensive testing in commercial herds using artificial insemination. The experience of poultry and mouse breeders in selection of breeding strains susceptible or resistant to leukemia should be carefully studied, not only in evaluating the genetic role in bovine leukemia but in other animals and man as well.

It was the insight and classic work of Rous, Bryan and others which contributed greatly to an understanding of viral tumorigenesis.[19] Experimentally it was demonstrated that Rous sarcoma tumor induction was dependent on dose, and genetic resistance was overcome if birds were inoculated with a high concentration of virus. The experimental animals that first developed tumors were found to have the highest concentration of recoverable virus. These factors undoubtedly do apply to an understanding of the mechanisms of leukemic disease in cows and might in part explain the high incidence in certain herds.

Several investigators have attempted to transmit bovine leukemia to other cattle by the use of neoplastic tissues or body fluids and most results have been negative. One of the main shortcomings of such research, however, has been inadequate numbers of both inoculated and control groups. Some investigators have reported that PL developed in inoculated cattle and in some cases was followed by tumor development. Results of one of our transmission studies, which was ended after six years, strongly suggest that a factor producing leukemia and persistent lymphocytosis was transmitted from inoculated cows to their calves.[36]

Thus far, attempts to demonstrate unequivocally a bovine leukemia virus by use of standard viral oncology methods have been unsuccessful. Previously, we demonstrated virus-like particles in electron microscopic thin sections of bovine leukemia tissue.[31] Recently, we were encouraged by demonstrating particles in plasma of two cows with spontaneous leukemia (Figure 1), but not in plasma of four normal cows. These particles in some ways resemble the typical "C" type viruses that we have demonstrated in plasma of spontaneous and experi-

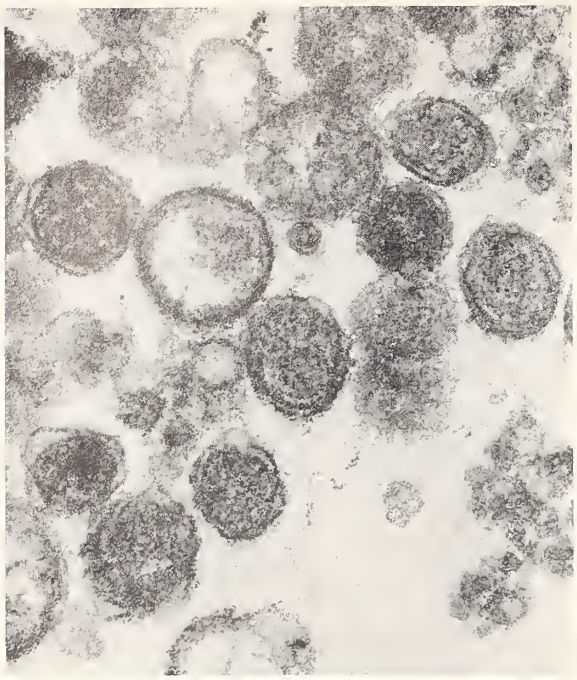


Figure 1.—Electron micrograph of a pellet obtained from plasma of a leukemic cow. 75,000 X.

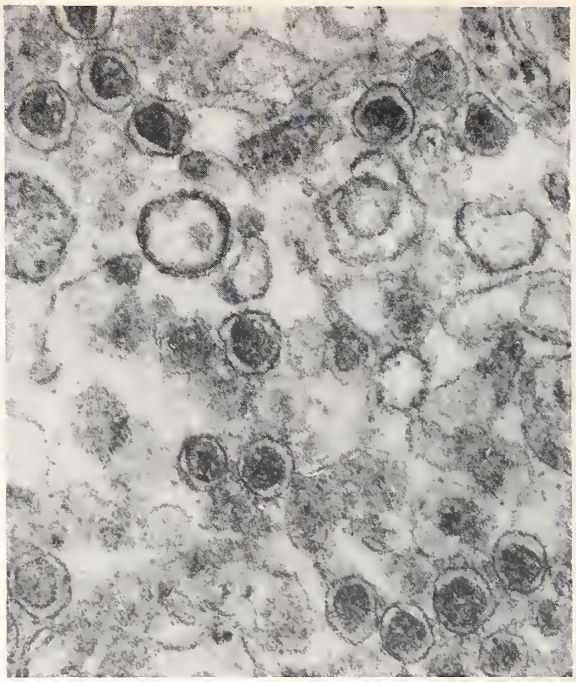


Figure 2.—Electron micrograph of a pellet obtained from plasma of a leukemic cat. 75,000 X.

mental cats with leukemia (Figure 2). However, their relationship, if any, to leukemia will be determined only after evaluation of their biological activity in inoculated calves.

Vigorous efforts also have been made to demonstrate causative leukemogenic agent(s) in man. Dalton[10] and Dmochowski[12] have described type "C" viral-like particles in thin sections made from human lymph nodes and leukemic plasma pellets. Recently, investigators demonstrated herpes virus-like particles[16] and Reo-virus[4] in cell cultures obtained from patients with Burkitt lymphoma. Whether these particles are related to the neoplastic disease is a question that cannot be answered until their biological activity is also ascertained.

Public Health Aspects

The vital question, of course, is whether bovine or other animal leukemia is in any way related to the disease in man. Epidemiologic studies conducted by Ringertz[30] in Sweden and Jensen[22] in Denmark have dealt with correlative incidence rates between human and bovine leukemia, and in most areas no correlation was found. Aleksandrowicz in Poland,[2] however, demonstrated a positive correlation. A preliminary collaborative study that we are carrying out with the State Department of Public Health in California may shed some light on this issue but it must be realized that epidemiologic studies will be difficult to design if human infection occurs during embryonic development or during the early neonatal period as it apparently does in some animal species.

We do not know whether the hypothetical bovine leukemia virus is in some way defective or masked, but if it is, it may act in a way similar to avian Rous sarcoma virus. The Rous virus, which is defective, has a wide host range and will produce hemorrhagic disease in rats,[1] sarcomas in mice, guinea pigs, hamsters and rabbits,[37] benign or malignant growths in Rhesus monkeys[26] and brain tumors in rabbits, hamsters[27] or neonatal puppies.[28] The Moloney murine sarcoma virus recently described[25] is also defective, but whether it will have a wide host range is still to be determined. However, the once held concept of tumor virus host specificity is no longer tenable.

Finally, one must also consider various responses of the host to the same tumor virus. Burmester and coworkers,[7] using different concentrations of virus and chickens of varying age and genotype induced a wide range of histologic types of tumors with inoculations of RPL-12 strain of avian lymphoid leukosis virus. Gross[18] also demonstrated a similar wide range of histologic cellular responses to a single inoculation of Passage A Gross murine leukemia virus. Therefore, it is be-

coming increasingly important to realize that tumor viruses have the potential to cause neoplasia in a variety of unrelated species and the induced tumors are not always histologically identical.

REFERENCES

1. Ahlström, C. G., Jonsson, N., and Forsby, N.: Rous sarcoma in mammals: Acta Path. Microbiol. Scand. Suppl., 154:127-129, 132-133, 1962.

2. Aleksandrowicz, J., and Janicki, K.: The epidemiology of leukemia in Poland with a special regard to the Cracow region, and its correlation with the cattle leukemia, Proc. 9th Congr. Eur. Soc. Hemat., Lisbon, Karger, Basel, New York, 1963, pp. 127-129.

3. Baker, C. G., Carrese, L. M., and Rauscher, F., Jr.: The special virus-leukemia program of the National Cancer Institute—Scientific aspects and program logic, In Some Recent Developments in Comparative Medicine, Symp. Zool. Soc. London, Academic Press, New York, 17, 1966, pp. 259-278.

4. Bell, T. M., Mossie, A., Ross, M. G. R., and Williams, M. C.: Isolation of a reovirus from a case of Burkitt's lymphoma, Brit. Med. J., 1:1212-1213, 9 May 1964.

5. Bendixen, H. J.: Skin leukosis in cattle in Denmark. Epidemiologic, clinical and patho-anatomic investigations, International Symposium on Comparative Leukemia Research, Hannover, Germany, 12 Aug. 1963.

6. Bierman, H. R., Marshall, G. J., and Winer, M. L.: The prediagnostic state of lymphoma: Detection and Description, JAMA, 186:185-192, 19 Oct. 1963.

7. Burmester, B. R., Gross, M. A., Walter, W. G., and Fontes, A. K.: Pathogenicity of a viral strain (RPL-12) causing avian visceral lymphomatosis and related neoplasms. II. Host-virus interrelations affecting response, J. Nat. Cancer Inst., 22:103-127, 1959.

8. Conner, G. H., LaBelle, J. A., Langham, R. F., and Crittenden, M.: Studies on the epidemiology of bovine leukemia, J. Nat. Cancer Inst., 36:383-388, 1966.

9. Croshaw, J. E., Jr., Abt, D. A., Marshak, R. R., Hare, W. C. D., Switzer, J., Ipsen, J., and Dutcher, R. M.: Pedigree studies in bovine lymphosarcoma, Ann. N.Y. Acad. Sci., 108:1193-1202, 1963.

10. Dalton, A. J., and Mitchell, E. Z.: Detection of viruses with the electron microscope; viruses inducing cancer Ed. By W. J. Burdette, University of Utah Press, Salt Lake City, 1966, pp. 237-249.

11. Dameshek, W., and Gunz, F.: Leukemia; Grune and Stratton, Inc., New York, 1958, pp. 1-11.

12. Dmochowski, L.: Electron microscope studies of leukemia in animals and men; In Current Research in Leukemia, Ed. by F. G. J. Hayhoe, Cambridge Univ. Press, 1965, pp. 22-33.

13. Dungworth, D. L., Theilen, G. H., and Lengyel, J.: Bovine lymphosarcoma in California. II. The thymic form: Path. Vet., 1:323-350, 1964.

14. Ellerman, V., and Bang, O.: Experimentelle Leukämie bei Hühnern. Centralbl.: Bakt. Abt. 1 (Orig.), 46: 595-609, 1908.

15. Englebreth-Holm, J.: Spontaneous and Experimental Leukemia in Animals: Oliver and Boyd, Edinburgh, 1942, pp. 3-51.

16. Epstein, M. A., Achong, B. G., and Barr, Y. M.: Virus particles in cultured lymphoblasts from Burkitt's lymphoma, Lancet, 1:702-703, 28 Mar. 1964.

17. Gross, L.: Spontaneous leukemia developing in C_3H mice following inoculation in infancy with AK-leukemic extracts, or AK-embryos, Proc. Soc. Exp. Biol., 76:27-32, 1951.

18. Gross, L.: Biological and pathogenic properties of a mouse leukemia virus, Acta Haemat., 23:259-275, 1960.

19. Gross, L.: Oncogenic Viruses, Pergamon Press, Oxford, 1961, pp. 56-70.

20. Hare, W. C. D., McFeely, R. A., Abt, D. A., and Feierman, J. R.: Chromosomal studies in bovine lymphosarcoma, J. Nat. Cancer Inst., 33:105-118, July 1964.

21. Jarrett, W. F. H., Martin, W. B., Crighton, G. W., Dalton, R. G., and Stewart, M. F.: Leukaemia in the cat, Nature, 202:566-568, 9 May 1964.

22. Jensen, N. K.: Topographical study of leukemia in Denmark: IX Int'l Cancer Congr., Abt. of Papers, 1966, p. 727.

23. Kawakami, T. G., Theilen, G. H., Dungworth, D. L., Beall, S. G., and Munn, R. J.: "C"-type viral particles in plasma of feline leukemia, Science, 158:1049-1050, 24 Nov. 1967.

24. Moldovanu, G., Moore, A. E., Frieman, M., and Miller, D. G.: Cellular transmission of lymphosarcoma in dogs, Nature, 210:1342-1343, 25 June 1966.

25. Moloney, J. B.: A virus-induced rhobdomyosarcoma of mice, Conference on Murine Leukemia, Nat. Cancer Inst. Mono., 22:139-142, Sept. 1966.

26. Munroe, J. S., and Windle, W. F.: Tumors induced in primates by chicken sarcoma virus, Science, 140:1415-1416, 1963.

27. Rabbotti, G. F., Raine, W. A., and Sellers, R. L.: Brain tumors (gliomas) induced in hamsters by Bryan's strain of Rous sarcoma virus: Science, 147:504-506, 29 Jan. 1965.

28. Rabbotti, G. F.: Brain tumors in puppies induced by Rous sarcoma high titer Bryan strain, Personal Communication, 1966.

29. Rickerd, C. G., Barr, L. M., Noronha, F., Dougherty, E., and Post, J. D.: C-type virus particles in spontaneous lymphocytic leukemia in a cat: The Cornell Vet., 57:302-307, Apr. 1967.

30. Ringertz, N.: The geographical distribution of leukemia and malignant lymphoma in Sweden: IX Int'l Cancer Cong., Abt. of Papers, p. 726.

31. Sorenson, G. D., and Theilen, G. H.: Electron Microscopic Observations of Bovine Lymphosarcoma: Ann. N.Y. Acad. Sci., 108, 1963; 1231-1240.

32. Theilen, G. H., Schalm, O. W., and Gilmore, V.: Bovine lymphosarcoma. Clinical and hematologic studies of lymphosarcoma in a herd of cattle, Am. J. of Vet. Res., 22:23-31, Jan. 1961.

33. Theilen, G. H., Appleman, R. D., and Wixon, H. G.: Epizootiology of lymphosarcoma in California cattle, Ann. N.Y. Acad. Sci., 108:1203-1213, 4 Nov. 1963.

34. Theilen, G. H., Dungworth, D. L., Lengyel, J., and Rosenblatt, L. S.: Bovine lymphosarcoma in California. I. Epizootiologic and Hematologic Aspects, Health Lab. Sci., 1:96-106, Apr. 1964.

35. Theilen, G. H., and Dungworth, D. L.: Bovine Lymphosarcoma in California. III. The Calf Form: Am. J. Vet. Res., 26 May 1965; 696-709.

36. Theilen, G. H., Dungworth, D. L., Harrold, J. B., and Straub, O. C.: Bovine lymphosarcoma transmission studies: Am. J. Vet. Res., 28:373-386, Mar. 1967.

37. Zilber, L. A., and Kryukova, I. N.: Haemorrhagic disease of rats due to the virus of chick sarcoma, Acta Virol., 1:156-160, 1957.

Occlusive Disease of the Vessels of the Aortic Arch

Diagnosis and Management

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■ *Physicians should be alert to the possibility of occlusion of one or more of the branches of the aortic arch in any patient having neurologic symptoms or complaint of claudication in the upper extremities. The finding of a pulse deficit in the neck or arm and a blood pressure difference of more than 30 mm of mercury between the two arms is pathognomic of this disease. The presence of the occlusive process can be confirmed and its extent determined by angiography.*

Vascular reconstruction can be expected to restore normal hemodynamics with gratifying relief of symptoms in the majority of cases.

THE CURRENT EMPHASIS on the prevention of strokes places the responsibility for early diagnosis of occlusive extracranial vascular disease with the physician. Previously hopeless victims of cerebral vascular insufficiency can now be treated effectively by vascular reconstruction provided the occlusion is in an accessible location in the neck. It is the purpose of this communication to describe the salient features in the diagnosis and management of arterial occlusion involving the vessels of the aortic arch. The symptoms and findings in occlusion of this type are so characteristic that a presumptive diagnosis can be established with a high degree of accuracy by history and physical examination alone.

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Occlusive disease of the vessels of the aortic arch was first recognized in 1856 by Savory[12] in a "young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated." Takayasu, an astute Japanese ophthalmologist, reported in 1908 on retinal changes secondary to occlusion of the great vessels of the neck and thereupon Takayasu's disease became an entity.[13] Martorell and Fabre[9] in 1944 reported from Barcelona on "the syndrome of obliteration of the supra-aortic trunks" and in Europe the designation Martorell-Fabre syndrome continues to be used.

Recently, investigators have tended to include all occlusive diseases of the vessels of the aortic arch in a single entity although the condition may be caused by any of several etiologic factors. The most common obstructive lesion found in the vertebral, carotid and subclavian arteries is an atheromatous plaque, with or without thrombosis. The

inflammatory arteritis of syphilis and a poorly understood nonspecific inflammatory lesion, as is present in Takayasu's disease, are found but rarely. Crawford and coworkers[4] reporting on 108 lesions in 67 patients, gave this interesting tabulation of the site of occurrence: left subclavian 45, innominate 24, left common carotid 23, right subclavian 15, right common carotid 1. In that series, 41 per cent of the patients had multiple arterial obstructive lesions. Hurwitt and associates noted that cerebral angiography has demonstrated arterial stenosis or occlusion of the vessels of the neck three times more often than cerebral tumors, five times more often than cerebral aneurysm and 15 times more than cerebral arteriovenous malformations.[8]

Subclavian Steal

One interesting aspect of obstructive lesions of the vessels of the aortic arch is the hemodynamic changes which may be present. Although suspected from the time of Willis (1664)[19] and suggested by Gray[6] in his anatomy text, the actual reversal of blood flow in a vertebral artery was first demonstrated by Contorni[3] in 1960. It was Reivich and coworkers[10] who clinically and experimentally showed the significance of the reversal of blood flow secondary to subclavian obstruction. Since this report in 1961 many investigators have confirmed these findings and the subclavian steal syndrome is now well recognized.[5] Not so well understood is why some patients with subclavian artery obstruction have symptoms of basilar artery insufficiency while some do not. Reivich[10] demonstrated that it requires approximately 10 per cent reduction in the subclavian artery mean pressure to cause reversal of vertebral flow. It takes 50 to 60 per cent occlusion of the lumen of a vessel to cause a decrease in flow through it.[7] The integrity of the circle of Willis is a critical feature and the atherosclerotic changes in the vessels of the neck may be present in these anastomotic vessels as well. Anatomic variations in the vertebral arteries are important. The right vertebral is small in about 10 per cent of people and absent in 3 per cent while the left vertebral is small in 6 per cent and absent in 2 per cent. Occlusion of the major supply to the basilar artery could be disastrous and may have been the cause of the rare serious complications reported following ligation of the vertebral artery.[14,17]

Experimental work on dogs has demonstrated that reversal of vertebral flow following occlusion of the proximal subclavian artery causes a 41 per cent overall reduction of cerebral blood flow. Exercise of the occluded extremity causes an abrupt increase in muscular blood flow and should therefore abruptly decrease basilar artery flow because of the reversal of vertebral flow, thereby producing basilar insufficiency. Clinically this is true and experimental work by Sammartino and Toole[11] with dogs confirms this chain of events.

Our experience with this problem consists of nine cases, two of which involved occlusion of the innominate artery and seven which involved the left subclavian artery with demonstrated subclavian steal.

Clinical Material

Table 1 summarizes the symptoms and findings in nine patients having occlusive disease of the branches of the aortic arch. There were five women and four men ranging in age from 43 to 75 years. The most common symptom was dizziness, which occurred in six of the nine patients. Claudication of the involved arm was present in five cases. A palpable pulse deficit was noted in eight patients. The difference in blood pressure between the two upper extremities ranged from 38 mm of mercury in the patient with the least disparity to 94 mm in the patient with the greatest. Visual blurring, hemiparesis and a neck bruit were present in four patients.

Seven of the nine patients in this report had angiographic proof of reversal of vertebral artery flow. In two patients who had brachiocephalic occlusions preoperative aortic arch angiography was not done. Decided narrowing (one patient) or complete occlusion (six patients) of the subclavian artery at or near its origin was observed radiographically and reversal of vertebral flow was noted in all seven cases. These findings were confirmed at operation.

Operative Considerations

The surgical approach employed in these patients was either a sternal splitting incision with extension into the neck along the anterior border of the sternocleidomastoid muscle or left anterolateral thoracotomy through the fourth intercostal space. The median sternotomy incision was extended in one patient (Case 1 in Table 1) up to the bifurcation of the common carotid artery for the removal of an additional occluding plaque in

TABLE 1.—*Summary of Nine Patients with Arterial Obstructions Aortic Arch*

Case	*Sex*	*Age*	*Symptoms*	*Findings*	*Blood pressure difference (mm of mercury)*	*Angiographic Findings*	*Operative Findings*	*Operative Procedure*	*Outcome*
1.	M	60	Dizziness Blurring of vision Transient blindness rt. eye Claudication rt. arm Transient lft. hemiplegia	Absent rt. carotid, brachial & radial pulses No bruits present over these vessels Ophthalmodynamometry: O.D. 0/0 O.S. 40/25	94	None performed	Partial innominate artery occlusion Total occlusion origin rt. subclavian artery Partial occlusion origin lft. internal carotid artery	Innominate & rt. subclavian endarterectomy with patch angioplasty. Rt. carotid bifurcation endarterectomy with patch angioplasty	Asymptomatic with equal blood pressures both arms Ophthalmodynamometry: O.D. 70/40 O.S. 65/35
2.	M	61	Dizziness Claudication rt. arm Transient blurring of vision	Absent rt. carotid, brachial & radial pulses	50	None performed	Partial innominate artery occlusion & total occlusion rt. subclavian artery	Innominate & rt. subclavian endarterectomy with patch angioplasty	Lft. hemiplegia, respiratory distress with cyanosis, hypotension & death. Autopsy severe pulmonary emphysema, fibrosis & atelectasis
3.	F	57	Stroke with rt. sided weakness 9 yrs. prior to hospital entry	Rt. facial weakness Bruit over lft. carotid artery at base of neck	50	Arch angiogram showed lft. subclavian obstruction with reversal of flow in the vertebral artery	Complete occlusion origin lft. subclavian artery	Lft. subclavian endarterectomy with patch angioplasty	Post op. blood pressures 110/80. Rt. arm 120/80. Lft. arm uneventful recovery
4.	F	43	Dizziness Claudication lft. arm	Weak lft. brachial pulse Bilat. carotid bruits	60	Arch angiogram showed lft. subclavian obstruction with reversal of flow in the vertebral artery	Complete occlusion origin lft. subclavian & partial occlusion lft. common carotid artery at origin	Bifurcation onlay graft from arch to distal subclavian artery & common carotid artery	Horner's syndrome left Blood pressure rt. arm 126/84 lft. arm 158/90
5.	F	57	Dizziness, tingling of lips & tongue, & lightheadedness made worse by exercise of lft. arm	Absent lft. radial pulse Bilateral carotid artery bruits	50	Arch angiogram showed obstruction of the lft. subclavian artery with reversal of flow in the vertebral artery	Complete occlusion origin lft. subclavian artery	Left subclavian artery endarterectomy with Dacron patch angioplasty	Restoration of equal pressures in both arms
6.	F	57	Numbness & weakness lft. face Numbness & weakness lft. arm	Absent lft. brachial & radial pulses	44	Complete lft. subclavian artery obstruction at origin with reversal of flow in the vertebral artery	Lft. subclavian artery occlusion at origin of this vessel	Lft. subclavian artery endarterectomy with Dacron patch angioplasty	Restoration of equal pressures in both arms Rt. asymptomatic Lft. Horner's syndrome
7.	M	63	Weakness, paresthesia & loss of fine motor function rt. hand with exercise, numbness rt. side of face & transitory speech difficulty	Weakness grip rt. hand Faint lft. brachial & radial pulses	40	One cm occluding plaque Lft. subclavian artery at the origin with reversal of vertebral artery flow	Complete lft. subclavian artery obstruction at the origin of this vessel	Lft. subclavian artery endartectomy with Dacron patch angioplasty	No pressure gradient between aorta & subclavian artery at completion of surgery. Blood pressure rt. arm 156/80 lft. arm 148/80
8.	F	75	Dizziness, blurring of vision & tingling paresthesia of the lft. side of face	Faint lft. radial pulse Systolic harsh bruit at the base of the neck on the lft.	38	Marked narrowing origin lft. subclavian artery with reversal of vertebral arterial flow	Arteriosclerotic plaque at origin lft. subclavian artery Pressure gradient between aorta & distal subclavian artery was 25 mm Hg.	Lft. subclavian artery endarterectomy with Dacron patch angioplasty	Restoration normal lft. subclavian flow with no gradient between the aorta & distal subclavian artery at completion of endarterectomy
9.	M	60	Episodes dizziness, syncope & diplopia. Prior transitory rt. hemiplegia	Faint lft. brachial & radial pulses	50	Complete lft. subclavian artery obstruction at origin with reversal artery flow	Lft. subclavian artery occlusion at origin of this vessel	Lft. subclavian artery endarterectomy with Dacron patch angioplasty	Restoration of equal pressures in both arms rt. asymptomatic

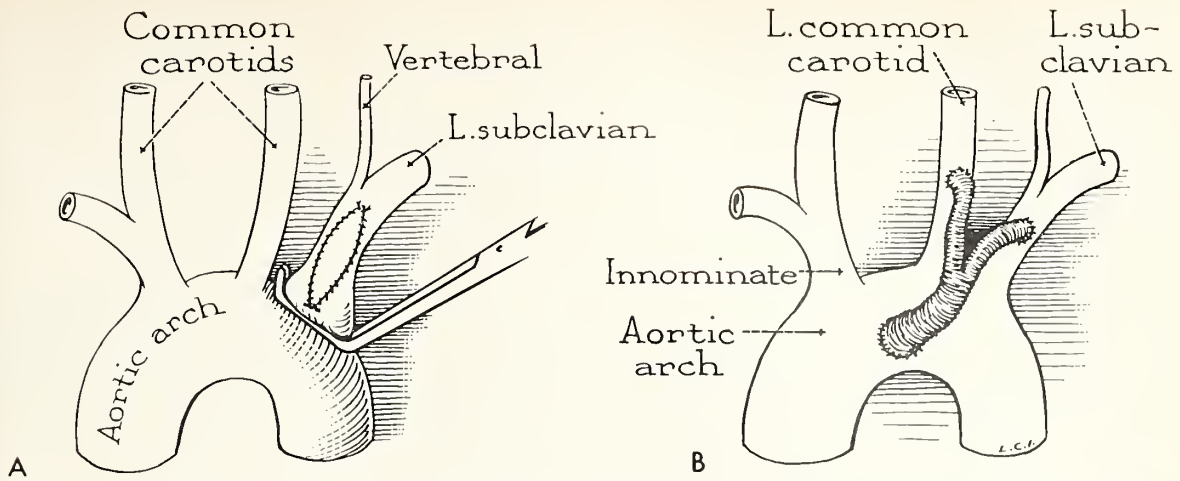


Figure 1.—*Left*, side aortic occlusion, endarterectomy and endogenous patch angioplasty. *Right*, bifurcation onlay prosthetic graft.

this location. Anterolateral thoracotomy was employed in two patients with occlusion at the origin of the left subclavian artery. These incisions were well tolerated and were associated with no morbidity. Closure of the sternum was accomplished with No. 25 stainless steel wire which gave maximum stability.

Endarterectomy followed by a small prosthetic (Dacron®) or autogenous vein patch angioplasty (Figure 1-A) was adequate in all but one of the patients. Extensive atherosclerotic involvement of the arch of the aorta in this particular patient made it necessary to employ a by-pass graft since side clamping of the aorta at the origin of the left subclavian artery also occluded the origin of the left common carotid artery. Reestablishment of the subclavian and left vertebral artery flow was done first by suturing in place a Dacron bifurcation graft to the aortic arch with anastomosis of one limb of the prosthetic vessel to the side of the subclavian vessel. A temporary polyvinyl shunt was placed within the common carotid artery while the posterior portion of the second limb of the bifurcation graft was sutured to this vessel. The shunt was removed and the anterior portion of the anastomosis was completed (Figure 1-B).

A Dacron or autogenous vein by-pass graft should be used between the aortic arch and the left subclavian artery for patients in whom the origins of the left common carotid and subclavian arteries are so close together that the application of a side occluding clamp to the aorta cannot be accomplished without occluding the carotid vessel. Such a shunt can be employed when it would be surgically difficult to expose the origin of the left subclavian artery. This operative procedure obviates inadvertent occlusion of the carotid artery and avoids injury to the aortic arch.

Results of Operation

The results of operation in these patients were excellent. Pulses were restored to the involved extremities and the difference in blood pressure gradient between the two arms was corrected. Weakness and claudication in the involved extremities were relieved and the vertigo and lightheaded feeling which had accompanied exercise of the arm disappeared. All patients were subjectively improved. The single postoperative death seemed unavoidable because of concomitant very severe chronic pulmonary disease. In retrospect the patient should not have been selected for operation.

In two patients Horner's syndrome developed after operation. Both had left subclavian occlusion and the damage to the cervical sympathetic nerves probably occurred as a result of mobilization of the proximal subclavian artery with interruption of nerve filaments from the inferior sympathetic ganglion which arch beneath the artery as Ansa subclavian fibers. In subsequent cases, great care has been taken not to damage sympathetic fibers in this area and the complication has not occurred.

Discussion

Occlusive disease of the branches of the aortic arch can produce several syndromes, depending upon the location of the lesion. Proximal subclavian or brachiocephalic occlusions with reversal

of vertebral artery flow give rise to basilar artery insufficiency. Symptoms here may be vague but usually include varying degrees of vertigo, nausea, numbness of the mouth, diplopia, dysphagia and dysarthria, paresis or paralysis of one to four extremities in any combination due to pyramidal tract involvement at the decussation. Exercise of the involved extremity ordinarily precipitates the patient's symptoms, since blood flow to the arm is abruptly increased with further demand for vertebral collateral flow. Dizziness was the most common complaint in our group of patients, a finding which parallels the observation of Wheeler,[18] who reported this symptom in 11 of 13 patients with aortic arch occlusions.

Occlusion of the carotid artery at its origin characteristically causes weakness or numbness of the contralateral extremities as well as ipsilateral blurring of vision or momentary blindness and contralateral homonymous hemianopsia. Four patients in this study complained of visual disturbance.

Brachiocephalic artery occlusion can give rise to an interesting clinical syndrome. Obstruction of the subclavian artery causes claudication of the right arm and occlusion of the common carotid artery at its origin on the right side gives rise to weakness and sensory changes in the left arm and leg as a result of cortical ischemia.

The physical findings in aortic branch occlusion are more specific and striking. There was a carotid or radial pulse deficit in eight of the nine patients in this series. Bryant and Spencer[1] called attention to this important finding in their report of 14 patients with occlusions of the branches of the aortic arch. There will be a blood pressure difference between the two arms of at least 30 mm of mercury, and some investigators believe that a difference of 20 mm should arouse suspicion of arterial occlusion.[11,15] In this study the blood pressure difference between the two arms ranged between 38 and 94 mm of mercury. Callow[2] emphasized the ease with which the diagnosis can be established when there is a pulse deficit and a disparity in blood pressure between the two arms. All patients but one in the present series had been heavy smokers for many years, suggesting that this may have been a factor in vascular injury.

Angiographic studies provide important information regarding the site and extent of the occlusion as well as whether reversal of flow is present in the vertebral artery. It is impossible to assess the degree of narrowing of an involved artery by palpation of the peripheral pulse.[16] The presence of an arteriosclerotic plaque in a vessel supplying the brain, even though minimal occlusion is present, may be the source for platelet or thrombotic emboli, resulting in cerebral symptoms and findings. Accurate angiographic delineation of such a plaque is helpful in the selection of patients for operation.

REFERENCES

1. Bryant, L. R., and Spencer, F. C.: Occlusive disease of subclavian artery, JAMA, 196:123-28, Apr. 1966.

2. Callow, Allan D.: Surgical management of varying patterns of vertebral-artery and subclavian-artery insufficiency, New Eng. J. Med., 270:546-52, 12 Mar. 1964.

3. Contorni, L.: Il circolo collaterale vertebro-vertebrale nella obliterazione dell arteria suclavia alla sua origine, Minerva Chir., 15:268, 1960.

4. Crawford, E. S., DeBakey, M. E., Morris, G. C., and Cooley, D. A.: Thrombo-obliterative disease of the great vessels arising from the aortic arch, J. Thorac. Cardiov. Surg., 43:38-53, Jan. 1962.

5. Editorial. A new vascular syndrome: "The subclavian steal." N. Eng. J. Med., 265:912, 1961.

6. Gray, H.: Anatomy: Descriptive and Applied, Twenty-second edition, Longmans, Green and Company, London, 1923, p. 636.

7. Heyman, A., Young, W. G., Dillon, M., Goree, J. A., and Klein, L. J.: Cerebral ischemia caused by occlusive lesions of the subclavian or innominate arteries, Arch. Neurol., 10:531-39, June 1964.

8. Hurwitt, E. S., Carton, C. A., Fell, S. C., Kessler, L. A., Seidenberg, B., and Shapiro, J. H.: Critical evaluation and surgical correction of obstructions in the branches of the aortic arch, Ann. Surg., 152:472-84, Sept. 1960.

9. Martorell, Otzet, F., and Fabre, T. J.: El sindrome de obliteracion de los troncos supra aorticos, Medicina Clin., Barcelona, 2:26-30, 1944.

10. Reivich, M., Holling, H. E., Roberts, B., and Toole, J. F.: Reversal of blood flow through the vertebral artery and its effect on cerebral circulation, New Eng. J. Med., 265:878-85, 2 Nov. 1961.

11. Sammartino, W. F., and Toole, J. F.: Reversed vertebral artery flow; The effect of limb exercise and hypertensive agents, Arch. Neurol., 10:590-94, June 1964.

12. Savory, W. S.: Case of a young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated, Tr. Med.-Chir. Soc., London, 39:205, 1856.

13. Takayasu, M.: Case of queer changes in the central blood vessels of the retina, Acta Soc. Ophthal. Jap., 12: 554, 1908.

14. Thomas, G. I., Anderson, K. N., Hain, R. F., and Merendino, K. A.: Significance of anomalous vertebral basilar artery communication in operations on the heart and great vessels, Surgery, 46:747, 1959.

15. Toole, J. F.: Reversed vertebral-artery flow; subclavian steal syndrome, Lancet, 1:872-73, 18 Apr. 1964.

16. Warren, R., and Triedman, L. J.: Pulseless disease and carotid artery thrombosis. Surgical considerations, New Eng. J. Med., 257:685, 10 Oct. 1957.

17. Webb, W. R., and Burford, T. H.: Gangrene of the arm following use of the subclavian artery in a pulmonosystemic (Blalock) anastamosis, J. Thorac. Surg., 23:199-207, 1952.

18. Wheeler, H. B.: Surgical treatment of subclavian-artery occlusions, New Eng. J. Med., 276:711-17, 1966.

19. Willis, T.: Practice of physick, S. Pordage, London, 1634, Part 6, p. 59.

Muscle Weakness and Atrophy

Clinical and Laboratory Evaluation

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■ *A thorough family history, the age at the time of onset and detailed information regarding the rate, mode of progression and distribution of weakness is needed for evaluation of patients with weakness and atrophy. Associated findings such as dermal lesions, tenderness, myotonia and fasciculations should also be noted.*

The major diagnostically useful laboratory tests are electromyography, nerve conduction, serum enzyme levels and muscle biopsy.

Each clinical and laboratory finding should be categorized in terms of its neuro-anatomical origin, since weakness may result from disturbances in the corticospinal pathways, the lower motor neuron, the myoneural junction and the muscle.

WEAKNESS IS THE predominant finding in most disorders of the skeletal muscle, but may also result from disturbances in the corticospinal pathways, the lower motor neuron including the anterior horn cell and its peripheral nerve, and the myoneural junction. The differential diagnosis of neuromuscular diseases depends primarily on a careful clinical history and physical examination[7,8] (Table 1), and laboratory tests may provide further valuable information.

The history should include a thorough family survey in search of any similar conditions and detailed information about the age of onset and the rate and mode of progression of the weakness (Tables 2 and 3). Clinical assessment should stress the distribution of weakness and the presence or absence of associated findings such as atrophy, hypertrophy, fasciculations, muscle tenderness, upper motor neuron signs, contractures, myotonia and dermal lesions (Tables 4 and 5).

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Each finding should be categorized in terms of its neuro-anatomical site[6] (Table 6). Weakness due to lesions in the corticospinal pathways rarely causes confusion in diagnosis with lesions of the lower motor neuron or muscle, since the presence of other signs of brain or spinal cord damage is readily recognized. Classical disease of the anterior horn cell is characterized by atrophy, fasciculations, hypoactivity or absence of reflexes, and usually a distal distribution of loss of strength. If the peripheral nerve is involved, associated sensory complaints are commonly present. Primary diseases of the muscle are also characterized by atrophy and diminution or absence of reflexes, but weakness is usually most severe in the proximal musculature. Myasthenia gravis, the only significant disorder associated with dysfunction of the myoneural junction, is usually characterized by involvement of the extraocular and bulbar musculature early in the disease process. In this disease there is little or no atrophy, and although the use of voluntary muscles is rapidly fatiguing, strength returns on rest. Due to its course, which is often variable, it may be mistaken for a psychogenic disturbance.

Indeed, the words *weakness, tiredness* and *fa-*

tigue obtained from the patient are quite vague and non-specific. They do not necessarily denote a disorder of the neuromuscular system but may relate to a conversion reaction or to depression or malingering. Psychogenic weakness, however, is usually accompanied by specific physical responses and inconsistencies.[12] A ratchet or cogwheel response is often found during manual muscle testing. In true neuromuscular weakness, the patient exerts maximal efforts throughout the test, and the weak muscles "give away" smoothly.

Inconsistencies also become apparent during the examination of the patient with psychogenic weakness or paralysis. During manual muscle testing in the recumbent position, the patient will be unable to resist a few pounds of force to the knee and hip flexors and extensors but be able to do deep knee bends without difficulty. Muscles which are apparently flaccid may suddenly contract when the patient performs functional or unusual movements such as crawling or walking backward. The patient with a conversion reaction may also perform many of the activities in a slow and laborious manner and frequently carries out simple acts with an overflow of activity into unrelated areas. The inconsistency is apparent since most of the functional tests such as knee bends require considerably more strength when done slowly.

Evaluation of weakness includes careful observation of the patient in a variety of positions and activities as well as an evaluation of individual muscle strength and range of joint motion. A thorough knowledge of functional anatomy is necessary since the patient with a slowly progressive neuromusculer disorder has often learned to substitute normal for weak muscle groups. To the inexperienced observer the resulting activity pattern will often appear to be completely normal.

Observation of the patient as well as details from the history can give valuable clues as to the distribution of weakness.[8] Loss of strength in the neck and trunk can be detected by the way the

TABLE 1.—*Steps in Clinical and Laboratory Evaluation of Weakness*

Detailed history
Family survey
Age of onset
Rate and mode of progression
Clinical assessment
Distribution of weakness
Tenderness
Contractures
Myotonia
Fasciculations
Upper motor neuron signs
Cramping
Hypertrophy
Dermal lesions
Myoedema
Mental retardation
General laboratory survey
Electromyography and nerve conduction
Serum enzymes
Biopsy

TABLE 2.—*Types of Inheritance in Disorders in which Weakness is the Predominant Feature*

Dominant
Facioscapulohumeral dystrophy
Myotonic dystrophy
Distal dystrophy
Proximal familial muscular atrophy
Peroneal muscular atrophy
Potassium periodic paralysis
Autosomal recessive
Infantile spinal muscular atrophy
Limb-girdle dystrophy
Peroneal muscular atrophy
Sex-linked recessive
Duchenne muscular dystrophy
Peroneal muscular atrophy

TABLE 3.—*Examples of Neuromuscular Disorders by Age at Onset*

Birth	Adults	
Infantile spinal muscular atrophy	Limb-girdle dystrophy	
Benign infantile hypotonia	Facioscapulohumeral dystrophy	
Congenital muscular dystrophy	Distal dystrophy	
Congenital myopathies	Motor system disease	
Early Childhood	Myotonic dystrophy	
Duchenne muscular dystrophy	Thyrotoxic myopathy	
Glycogen storage disease	Potassium periodic paralysis	
Infantile spinal muscular atrophy	Sarcoid myopathy	
Congenital myopathies	Peroneal muscular atrophy	
Late childhood and adolescence	Proximal familial muscular atrophy	
Limb-girdle dystrophy	Any age	
Congenital myotonia	Trichinosis	
Potassium periodic paralysis	Dermatomyositis and polymyositis	
Peroneal muscular atrophy	Polyarteritis	
	Myasthenia gravis	
	Drug-induced myopathy	

TABLE 4.—*Examples of Neuromuscular Disorders by Chief Site of Weakness*

Proximal muscle groups	
Muscular dystrophies	Myositis
Thyrotoxic myopathy	Sarcoid myopathy
Familial proximal muscular atrophy	
Distal muscle groups	
Motor system disease	Peroneal muscular atrophy
Myotonic dystrophy	Distal muscular dystrophy
Other peripheral motor neuropathy	
Proximal or distal or both	
"Floppy infant"	Myasthenia gravis
Poliomyelitis	Periodic paralysis
Steroid myopathy	Dystrophic ophthalmoplegia

TABLE 5.—*Findings Often Associated with Disorders in Which Weakness is the Predominant Feature*

Fasciculations	Lower motor neuron diseases
Congenital absence of muscles	Muscular dystrophy
Congenital contractures	Arthrogryposis
Frontal baldness, cataracts, testicular atrophy and myotonia	Myotonic dystrophy
Mental retardation	Duchenne dystrophy, myotonic dystrophy
Electrocardiogram abnormalities	Duchenne dystrophy, myotonic dystrophy, facioscapulohumeral dystrophy
Myotonia	Paramyotonia, myotonic dystrophy, congenital myotonia
Pseudohypertrophy	Muscular dystrophy
Muscle cramping	Myoglobinuria, McArdle's syndrome
Muscle tenderness and dermal lesions	Myositis
Myoedema	Myxedema

patient lifts his head from the pillow or rolls over in bed. In myasthenia gravis the masseter and temporalis muscles may fatigue quickly during chewing. If the orbicularis oculi are involved the patient may complain that he gets soap in his eyes when washing his face. The inability to whistle or to puff out the cheeks are further clues to facial weakness. If the patient is unable to comb her hair or apply lipstick, weakness of the proximal shoulder girdle muscles should be suspected. On the other hand, if she is not able to turn a doorknob or open a jar, distal muscle groups may be involved. Difficulty in crossing one knee on the other, or in arising from a chair or climbing stairs is often an early indication of weakness in the hip and thigh muscles. Foot drop, manifested by stumbling, or the inability to walk on the forefoot, indicates involvement of the distal muscles in the lower extremity. Careful observation of the patient's gait facilitates recognition of specific patterns of weakness. Pathologic locomotion may result from lesions in the upper or lower motor neuron as well as in the muscular system, and each category can often be identified by specific gait patterns that are consistent with the pathologic changes.[12]

TABLE 6.—*Evaluation of Weakness by Anatomical Area*

Corticospinal pathways	Hyperactive stretch reflexes. Increased resistance to passive motion. Abnormal reflexes. Weakness usually greater than atrophy.
Lower motor neuron	
Anterior horn cell	Fasciculation. Hypoactive or absent reflexes. Usually distal or generalized distribution. Atrophy usually in proportion to weakness.
Peripheral nerve	Above plus sensory changes
Myoneural junction—myasthenia gravis	Extraocular musculature usually involved. Fatigue easily following contraction. Strength increases following rest. Variable and fluctuating course.
Muscle fiber	Hypoactive or absent reflexes. Atrophy usually in proportion to weakness. Usually proximal distribution.
Functional	Cogwheel response. Inconsistencies. Hoover sign. Bizarre gait. Slowness of motion. Overflow of activity.

The clinical examination should be supplemented by serial measurements of muscle strength, range of motion, muscle bulk, activities of daily living and physical capacity. An excellent method of assessing the over-all strength of multiple

muscles is by means of functional testing in which the patient's classification is based on the ability and methods used in activities concerned with elevation and ambulation.[11] Such a simple classification can be placed on a reproducible, semiquantitative basis by timing the performance of standard test activities.

Evaluation of weakness in infants and young children is especially difficult and involves a thorough knowledge of normal growth and development. Weakness or hypotonia due to lesions in the corticospinal pathways, cerebellum and brain stem is not always accompanied in early life by exaggerated tendon reflexes, spasticity or pathologic reflexes.[13] Examples of such lesions are early atonic diplegia and congenital athetosis or cerebellar ataxia. Muscular weakness and hypotonia are not always distinguishable since weakness due to a lesion of the distal motor neuron or muscle fiber is often accompanied by hypotonia. This is, however, only true at rest, and there is a pronounced difference in strength between, for example, a child with muscular dystrophy and one with infantile spinal muscular atrophy when an attempt is made to voluntarily contract the muscles.

Before the examination it is necessary to put the child in such a position that the muscle group being tested can lift the appropriate part of the body against gravity. In addition, the muscle group must be made to contract or spontaneously move.[4] During the first six months of life, the various attitudinal reflexes may be utilized to elicit the desired muscle function. The asymmetrical tonic neck reflex demonstrates knee and elbow flexion and extension; Landau's reflex will elicit weakness of the hip, neck and trunk extensors; the grasp reflex can be used to determine weakness of finger flexion; and the Moro reflex will include the involvement of one extremity.

If motor activity is not spontaneously present, noxious stimuli may be used to produce withdrawal. When motor activity is present, relative weakness may be determined by any of several methods. The weak extremity will often resist movement with less force when rapid alternating passive movement is superimposed on spontaneous activity. Information may be obtained by restraining the spontaneous activity of an extremity and noting the force which tends to continue the motion. The shoulder adductors and scapular stabilizers can be tested by lifting the child under the armpits, since the normal spontaneous response is to push down against the examiner's fingers with surprising force. Arm and neck weakness may be determined by pulling the infant from a supine to a sitting position. The weak extremity will straighten out while the normal arm will flex at the elbow. Ambulation and locomotion patterns should also be observed.[5] When ambulation is delayed, abnormal patterns of locomotion—such as rolling, asymmetric crawling, scooting and hitching—are often used to substitute for normal walking. Close observation of these patterns may help in more precise identification of areas of weakness. Hitching, for example, can be performed only with stability of the trunk and upper extremities.

Laboratory Survey

Following the clinical evaluation, a general laboratory survey is indicated especially with reference to thyroid dysfunction, adrenocortical hyperfunction, serum potassium abnormalities, and the response of weakness to edrophonium chloride (Tensilon®). The major diagnostically useful laboratory tests are electromyography, nerve conduction, serum enzyme levels and muscle biopsy. Measurement of serum enzymes and electromyography should be done before the biopsy.

Enzymes such as the glutamic oxaloacetic and glutamic pyruvic transaminases (GOT and GPT), lactic dehydrogenase (LDH), aldolase, and creatine phosphokinase (CPK) are normally present in muscle and other tissues. Increased levels in the serum merely reflect an accelerated release from damaged or diseased tissues. The value of serum enzymes for the diagnosis of muscular diseases depends upon the integrity of other organs, since most enzymes are not specific to muscle and can be elevated in many other diseases. CPK, therefore, has emerged as the most reliable and sensitive chemical indicator of muscle fiber breakdown. Its main advantage is its limited distribution in the human body: It is found in far greater quantity in striated muscle than in any other tissue. The only other common cause of elevation of this enzyme in the serum is acute myocardial disease.

Enzyme levels are elevated in the more rapidly progressive kinds of dystrophy, such as the Duchenne type, and are highest early in the disease.[2] (Table 7). The increase in levels is not constant, however, and the age of the patient and the duration of the disease are factors capable of diminishing enzyme levels in patients with muscular dystrophy. As in many other tests, serial meaurements

TABLE 7.—*Serum Measurements of Creatine Phosphokinase (CPK) in Disorders in which Weakness is the Predominant Feature*

	Levels Elevated
Corticospinal pathways	..
Lower motor neuron	..
Myoneural junction-myasthenia gravis	..
Muscle:	
Duchenne dystrophy	+++
Limb-girdle dystrophy (early)	++
Limb-girdle dystrophy (late)	+
Facioscapulohumeral dystrophy	±
Myotonic dystrophy	±
Distal dystrophy	..
Acute myositis*	+++
Chronic myositis*	+
Congenital myopathies	±
Thyrotoxic myopathy	±

*Transaminases and aldolase often show a greater elevation than CPK.

reduce the chance of error. All of the enzymes, especially the transaminases and aldolase, are increased in dermatomyositis and polymyositis. The degree of rise is generally proportional to the disease activity, and essentially normal levels are often found in chronic myositis or after several weeks of steroid therapy. Little or no enzyme elevation occurs in lesions of the corticospinal pathways, anterior horn cell or peripheral nerve.[3] Occasionally, slight increases in CPK are found in thyrotoxic, nemaline and myotubular myopathy, periodic paralysis, myasthenia gravis and myotonic and facioscapulohumeral dystrophy. Moderate elevations are common in limb-girdle dystrophy when it occurs at an early age. Serum enzyme elevations may also occur in other conditions involving muscle alterations, such as physical exercise, myoglobinuria, surgical operations and crush injuries.

The electromyogram and nerve conduction, when abnormal, provide valuable but not diagnostically specific etiologic information about the weakness (Table 8). Both are normal in patients with lesions of the corticospinal pathways. Electromyograms are usually normal in myasthenia gravis, although findings similar to those observed in myopathy may be found in the late phases of the disease. Of greater significance is the observation that action potentials picked up from muscles that are stimulated with a repetitive current show a rapid diminution in amplitude as stimulation is continued.[1] In normal persons there is no appreciable difference in the amplitude of the response to either a tetanic or twitch stimulation. In some persons the potential amplitude increases rapidly with tetanic stimulation. This finding is regarded as highly suspicious of intrathoracic malignant disease.[10]

The principal contribution of electromyograms in diagnosis of atrophy and weakness due to lesions of the anterior horn cell or peripheral nerve, is the detection of denervation and its anatomic distribution.[9] Denervation is characterized by fibrillation potentials, usually accompanied by sharp waves. Fasciculation potentials may also be found in neuropathic diseases especially when the anterior horn cell is involved. The electromyogram cannot differentiate between lesions of the anterior horn cell and those of the anterior root and the peripheral nerve. To make this distinction, the peripheral nerve conduction velocity or latency is necessary. For example, in anterior horn cell disease such as poliomyelitis, the conduction velocity of the surviving motor nerve fibers is not substantially reduced. In patients with polyneuropathy, however, decided slowing is usually found.

The primary usefulness of electromyograms in evaluation of diseases of the muscle is the detection of abnormal motor units during attempts at volitional contraction. This usually takes the

TABLE 8.—*Electromyographic Findings in Diseases in which Weakness is the Predominant Feature*

	Fibrillation	*Sharp Waves*	*Myotonic Discharges*	*Voluntary Units Amplitude*	*Voluntary Units Duration*
Corticospinal pathways	absent	absent	absent	normal	normal
Lower motor neuron	+++	+++	absent	increased	increased
Myasthenia gravis	absent	absent	absent	usually normal	usually normal
Muscle:					
Dystrophy (early)	rare	rare	absent	often normal	reduced
Dystrophy (far advanced)	+	rare	absent	reduced	reduced
Polymyositis	++	+	pseudo-myotonic discharges	reduced	reduced
Congenital myotonia	absent	absent	+++	normal	normal
Myotonic dystrophy	rare	rare	+++	reduced	reduced

form of a diminution in duration and a reduction in voltage. Often a moderate increase occurs in the incidence of short-duration, low-voltage polyphasic potentials; and frequently there is a low-voltage interference pattern. Fibrillation potentials, with the patient at rest, are not unusual in such diseases as muscular dystrophy and are quite common in polymyositis. Uusally, however, fibrillation is not accompanied by sharp waves in myopathic disorders. Another pattern of potentials is that produced in disorders in which myotonia is a factor. These are characterized by a rapid volley of potentials which wax and wane at a very high frequency.

Muscle Biopsy

The muscle biopsy is the most valuable test in the differential diagnostic study of weakness. The significance of the biopsy, however, depends completely on the care exercised in selecting the muscle from which the specimen is to be taken, the surgical techniques employed, the size of the specimen and the methods by which the tissue is processed for histologic examination.[8] Biopsy of muscle is usually done to differentiate between the various myopathic and neuromyopathic causes of muscular atrophy and weakness or to delineate a generalized disease which only incidentally affects the muscle fibers or the interstitial tissues of muscles (Table 9).

TABLE 9.—*Comparison of Major Histologic Findings During Active Phase of Common Neuromuscular Disorders*

	Muscular Dystrophy	*Polymyositis*	*Neurogenic Atrophy*
Random muscle-fiber atrophy	++	++	..
Group (motor unit) atrophy	..	..	++
Muscle-fiber hypertrophy	++	±	±
Muscle-fiber regeneration	±*	++	..
Central nucleation	++**	+	..
Focal necrosis and phagocytosis	±*	++	..
Inflammatory cell infiltrate	±*	++	..
Connective-tissue proliferation	++	+ to ++	.. (+ late)
Fat-cell proliferation	+ to ++	+	.. (+ late)
Vasculitis	..	+ to ++	..

*May be found early in Duchenne dystrophy.
**Most common in myotonic dystrophy.

In infantile hypotonia, it is often impossible to differentiate among several possibilities without histologic identification. If there is a histologic pattern of group muscle-fiber atrophy surrounded by normal fibers, infantile spinal muscular atrophy is most likely. If there is random muscle fiber atrophy, hypertrophy and regeneration with central nucleation, endomysial connective tissue proliferation and fat-cell proliferation, muscular dystrophy should be considered. A diagnosis of benign congenital hypotonia is probable if the fibers appear to be normal in every respect, although atonic diplegia and severe mental retardation must also be excluded.

Clinically, confusion may also arise between polymyositis with a slow and insidious onset without the characteristic dermal lesions, and limb-girdle muscular dystrophy without a family history. Histologically, random muscle-fiber atrophy may be found in either condition. Polymyositis, however, usually shows less muscle-fiber hypertrophy, central nucleation and fat-cell proliferation and a greater degree of muscle-fiber regeneration and focal necrosis, inflammatory cell infiltration and vasculitis. Occasionally, it is impossible to decide whether the problem is one of slowly progressive dystrophy or polymyositis. A trial of corticosteroids may help in the differentiation.

Weakness is usually proximal in myopathy and distal in neuropathy. Results of biopsy, however, are often crucial in the exceptional rare cases of proximal heredofamilial juvenile muscular atrophy and the equally rare distal form of muscular dystrophy.

REFERENCES

1. Bauwens, Philippe: Introduction to electrodiagnostic procedures, *In:* "Electrodiagnosis and Electromyography," S. Licht, Baltimore, Waverly Press, 1961, pp 171-198.

2. Fowler, Jr., W. M., and Pearson, C. M.: Diagnostic and prognostic significance of serum enzymes. I. Muscular dystrophy, Arch. Phys. Med., 45:117-130, Mar. 1964.

3. Fowler, Jr., W. M., and Pearson, C. M.: Diagnostic and prognostic significance of serum enzymes. II. Neurologic diseases other than muscular dystrophy, Arch. Phys. Med., 45:125-130, Mar. 1964.

4. Johnson, Ernest W.: Examination for muscle weakness in infants and small children, JAMA, 168:1306-1313, Nov. 1958.

5. Johnson, E. W., and Spiegel, M. H.: Ambulation problems in very young children, JAMA, 175:858-863, Mar. 1961.

6. Magee, Kenneth R.: Clinical and pathological observations in neuromuscular disease, A review, Univ. of Mich. Med. Bull., 28:94-105, Mar.-Apr. 1962.

7. Pearson, Carl M.: Differential diagnosis of neuromuscular disease by clinical evaluation, Arch. Phys. Med., 47:122-125, Mar. 1966.

8. Pearson, C. M., and Price, H. M.: Muscle biopsy: Why? How? and When?, Hospital Medicine, 2:34-38, No. 4, Feb. 1966.

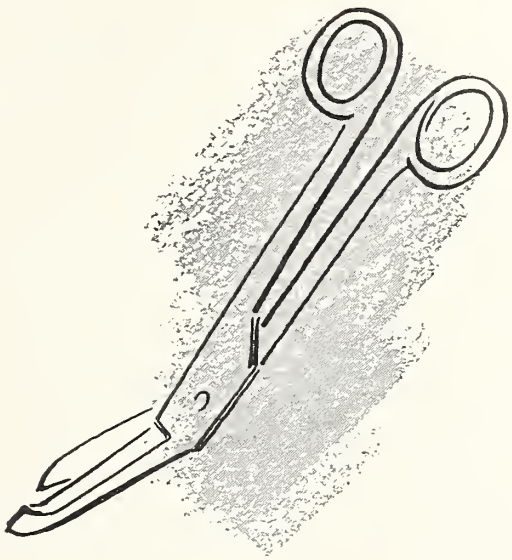
9. Rodriguez, A. A., and Oester, Y. T.: Fundamentals of electromyography, *In:* "Electrodiagnosis and Electromyography," S. Licht, Baltimore, Waverly Press, 1961, pp 286-341.

10. Eaton, L. M., and Lambert, E. H.: Electromyography and electric stimulation of nerves in diseases of motor unit, JAMA, 163:1117, Mar. 1957.

11. Vignos, Jr., P. J., Spencer, Jr., G. E., and Archibald, K. C.: Management of progressive muscular dystrophy of childhood, JAMA, 184:89-96, Apr. 1963.

12. Worden, R. E., Johnson, E. W., and Burk, R. D.: Diagnosis of hysterical paralysis, Arch. Phys. Med., 42:122-123, Feb. 1961.

13. Zellweger, Hans: General aspects of muscular hypotonia, Am. J. Phys. Med., 40:177-182, Oct. 1961.



Failure to Thrive

An Analysis of 83 Cases

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■ *The case histories of 83 children admitted to the hospital with a diagnosis only of failnre to thrive were examined. In twenty-six cases there was evidence of maternal deprivation as a factor. Forty patients were found to have significant organic diseases as a possible or probable cause or contributing inflnence.*

Twenty-six were found to have some degree of mental retardation, either documented or suspected, but in nearly all of them there were associated factors presumably responsible, at least in part, for failure to thrive.

Several children had birth weight less than 2,500 grams, but no child was thought to grow poorly because of prematurity alone. Congenital anomalies such as cleft palate and other problems leading to feeding difficulties were not unusnal.

In any case of persistent failnre of an infaut to gain adequately in weight and length, in which the cause is not evident, the child should be admitted to a hospital to determine respouse in a new environment. Also an adequate social history should be sought and siblings more closely evaluated; and carefnl study should be made of the renal, gastrointestinal, cardiac, pulmonary and central nervous systems, even if there are no symptoms or signs referable to these systems.

FAILURE TO THRIVE is defined here as lack of adequate growth in height and weight of a young infant or child for reasons that are not immediately apparent to the examining physician.

Growth failure is often associated with a well defined disease, such as cystic fibrosis of the pancreas, congenital renal disease, congenital disease of the heart, dystrophy of the osseous system and disorders of the endocrine system. In these disorders the nature of the associated disease is clear, although the cause of the growth deficiency and the mechanisms responsible for the growth retardation are not always known. In such cases the underlying disorder, such as congenital disease of

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the heart, is considered primary and the growth failure is considered to be an associated phenomenon. Patients falling into these categories may experience improvement in the rate of growth if the disease is successfully treated.

The purpose of this communication is to present a study of a group of infants and children with growth failure which was not associated with an obvious disease and the cause of which was not evident to the examining physician. The progress of these patients was followed during the period they were in hospital, and subsequently for varying periods, to determine what diagnosis, if any, was made during the stay in hospital or after a long period of follow-up. As a result of this study of some 83 cases, certain general conclusions have been drawn which may serve as guides to physicians confronted with cases of growth failure of unknown cause in infancy.

In order to select cases for the study, it was decided to include only those patients who were admitted to the hospital with the diagnosis of failure to thrive of unknown cause after thorough examination by a pediatrician. The admission procedures of this hospital require that the infant be seen by a pediatrician at least once before admission to the hospital. Most of the children were seen by several physicians before admission. The validity of this method of selection of patients is borne out by the fact that virtually none of the infants admitted to the study turned out to have a disease falling into one of the categories mentioned above as frequently associated with growth retardation. The screening procedures to which such infants were subjected before admission were sufficient in the vast majority of cases to exclude the diseases commonly associated with failure to thrive. The method of selection of cases, therefore, provided patient material which was representative of the problem as a whole.[1,13]

Materials and Methods

The case records of all children who were admitted to Children's Hospital of Los Angeles over a period of two and a half years with the "diagnosis" of failure to thrive as the reason for admission were selected for review. All patients had been seen by a physician before admission. The subsequent course of these children was examined to determine what, if any, causative factors were found for retardation of growth. Children admitted with the primary diagnosis of organic disease of the heart, lungs, pancreas or other organs and with a secondary diagnosis of growth failure were not included in the study. In order to determine the growth pattern of the children after discharge from the hospital, further information was obtained by (1) asking the patients to return for additional history and examination, (2) sending to the private physician a letter asking for his evaluation of the physical and mental development and for other pertinent facts in the medical history of the patient, or (3) correspondence or telephone conversations with parents or health agencies, requesting physical measurements of the children and other pertinent medical facts. The patients were finally categorized into five groups, although there was considerable overlap. The groups were as follows:

1. *Organic Disease Group.* This group was subdivided into acute and chronic illness categories and an attempt was made to ascertain if the organic illness was the cause of the failure to thrive. Children with mental retardation with or without evidence of other diseases were arbitrarily included in this group.

2. *Maternal Deprivation Group.*[9,10] This term is used in preference to *environmental deprivation,* although the mother may not have been the only person whose emotional influence was denied the child. These children grew inadequately in their usual environment but experienced more rapid growth after admission to the hospital or during periods of close supervision after the hospitalization. None of them had evidence of chronic organic disease, and improvement in growth rate was out of proportion to the results expected from medical therapy. It was frequently impossible to determine with certainty what environmental factor was lacking, but often there was overt evidence of improper feeding, malnutrition or parental neglect.

3. *Idiopathic Group.* No satisfactory reason for growth retardation was discovered in these children, despite careful study during hospitalization.

4. *Unclassified Group.* Some of the children with growth retardation could not be put into any of the other categories because the period of observation was very short or incomplete.

5. *Growth Retardation with Low Birth Weight Group.* Any child with a birth weight of less than 2,500 grams was included in this group, in addition to being classified in one of the above groups. This additional category was established to assess the role of prematurity or intrauterine growth

TABLE 1.—*General Information on 83 Patients with "Failure to Thrive"*

Group	No.	Male	Female	Median Age (mo.)	Number Referred by Physician	Deceased	Follow-up: Over 6 mo.	Follow-up: 3-6 mo.	Follow-up: Under 3 mo.	Median Length Follow-up (months)
Organic disease	40	23	17	4	31	5	34	2	4	22
Maternal Deprivation	26	15	11	5	8	1	18	2	6	18
Idiopathic	10	7	3	5	7	0	8	2	0	21
Unclassified	7	4	3	3.75	3	0	0	0	7	0.5
TOTAL	83	49	34	4	49	6	60	6	17	18

Infants with low birth weight are included in these four groups.

retardation as a primary or contributory cause of failure to thrive.

Results

The case histories of 83 children were reviewed. There were 49 males and 34 females, first seen at a median age of four months. Physicians in private practice referred 49 of the patients, and 34 came from the Out-Patient Department at Children's Hospital. Sixty were examined over periods of six months or longer, and the median follow-up period was 18 months (Table 1). Six children died while in hospital or during the follow-up period. Of these, five were known previously to have severe organic disease, and the sixth, who had no known disease, but who was included in the maternal deprivation group, was found dead in his crib at home. No information as to the cause of death could be obtained.

Twenty-seven of the 83 children had a significant degree of mental retardation (Table 2). The majority were evaluated by a standard intelligence testing. In some the retardation was so extreme that objective testing was considered unnecessary. Two had mental retardation as the only obvious factor related to their failure to thrive. Fourteen had associated organic defects and five were assigned to the maternal deprivation group. Six of the children were thought to have possible mental retardation but, for various reasons, adequate evaluation could not be carried out.

Organic Disease Group

Children exhibiting failure to thrive who had organic disease were generally very young when first seen. Sixteen of the 40 infants and children were less than three months of age when they were first admitted to the hospital. Except for a nine-year-old girl with celiac disease, the age range of the subjects when first seen was one day to ten months, and the median was four months. Many had an acute illness which in general did not retard their growth after treatment. The question whether organic disease was the probable or possible cause of growth failure has been difficult to resolve and an arbitrary differentiation had to be made, taking into account the nature and length of the illness, the age and the subsequent growth pattern. There were 23 males and 17 females in this group.

Twenty-nine of the children were kept under observation for a period of one year or more. Where the period was less than one year, the change in growth pattern generally paralleled the severity of the underlying disease. The types of illness in children falling into this category are listed in Table 3. In five cases the disease was considered as a possible cause of the failure to thrive, and in the remainder the disease was considered to be the probable cause. Electroencephalograms were reported as being within normal limits in two patients with mental retardation and abnormal in seven cases. Electroencephalographic tracings taken on three other children without mental retardation were reported as being abnormal in one who had a history of minor motor seizures, and within normal limits in the other two. Unless there was reasonably successful treatment of the organic

TABLE 2.—*Distribution of Patients with Mental Retardation among the Various Groups*

Mental Retardation	D.Q.	Organic Disease	Maternal Deprivation	Idiopathic	Short Follow-up	Total
Severe	50	10	1	..	..	11
Moderate	50-70	3	2	..	1	6
Mild	70-80	1	2	1	..	4
Possible	..	1	2	2	1	6

D.Q.—developmental quotient.

TABLE 3.—*Organic Diseases Found in Patients with Failure to Thrive*

		Number
I.	*Diseases of the Central Nervous System* (all with mental retardation)	
	Mental retardation, no other findings	2
	Mental retardation with cerebral palsy	1
	Mental retardation with cerebral palsy and microcephaly	1
	Mental retardation with cerebral palsy and a skull fracture at birth	1
	Maternal rubella syndrome with microcephaly and prematurity	1
	Down's syndrome with congenital heart disease	1
	Hydrocephalus, arrested	1
	Partial cleft palate	1
	Neurogenic dysphagia	1
II.	*Gastro-Intestinal System*	
	Chronic enterocolitis, fatty liver and pancreatic fibrosis	1
	Pyloric stenosis	1
	Glossoptosis with micrognathia	1
	Rumination	2
	Rumination with cleft palate	1
	Ischiorectal abscess	1
	Cardio-esophageal chalasia	1
	Cleft palate with imperforate anus and perineal fistula	1
	Infectious hepatitis	1
	Celiac syndrome	1
III.	*Respiratory System*	
	Chronic pneumonia (pneumocystis carinii?)	1
	Interstitial pneumonia	1
	Mucoviscidosis and asthma	1
	Mastoiditis and otitis media	1
	Chronic tonsillo-adenoiditis	1
	Peribronchial pneumonia	1
	Chronic sinusitis with intolerance to milk and wheat	1
	Chronic diarrhea with mastoiditis and otitis	1
	Chronic maxillary sinusitis	1
IV.	*Urinary Tract*	
	Pyelonephritis with chronic cystitis	1
	Pyelonephritis with pneumonia	1
	Pyelonephritis with ureteral hypotonia	1
	Pyelonephritis, E. coli diarrhea and ureteral stricture	1
V.	*Cardiovascular System*	
	Endocardial fibroelastosis	1
	Atrio-ventricular cushion defect (see also 2 cases of disease of the central nervous system)	1
VI.	*Miscellaneous*	
	Idiopathic hypercalcemia with mental retardation	1
	Vibrio bacteremia	1
	Icthiosiforme erythroderma and prematurity	1
	Hypogammaglobulinemia and bladder neck obstruction	1
		40

disease, no remarkable gain in weight was noted during the period in hospital. Two of the children who had significant organic disease, but who were probably given inadequate care in the home (patients with celiac disease and with pyelonephritis and chronic cystitis), gained significantly during each stay in the hospital.

Skeletal maturation was measured in 12 instances and was considered within normal limits in eight. Two children with severe mental retardation — one of whom had "chronic tonsilloadenoiditis," and the other cleft palate and ectopic anus — showed evidence of significant retardation of skeletal age.

Maternal Deprivation Group

Twenty-six of the 83 children were considered to qualify for the diagnosis of maternal deprivation. Many of these infants and children gained weight rapidly while under observation in the hospital or rehabilitation center. In others a rapid weight gain was observed when the infant or child was transferred to an environment different from that in which he existed during his period of failure to thrive. Significant weight gain in these circumstances was considered to be at least 1.5 ounces per day during the initial period of observation in the infants under six months of age and at least 1 pound a month in older infants during the period of observation.

The group consisted of 15 boys and 11 girls. In 18 of the children in this group, observations extended for a period greater than six months. As was previously mentioned, one child who was followed for a short time (two months) was subsequently found dead in his crib. He had gained 52 ounces during two periods in hospital which comprised a total of 26 days. Another child once had been admitted to hospital with a diagnosis of traumatic cerebral injury and subarachnoid hemorrhage before his admission for the complaint of failure to thrive. In many cases the medical historian recorded that the mothers beat the children. Two mothers abandoned their families, two mothers were ill with seizures (probably psychomotor), one mother was admitted to an institution for schizophrenia and another killed herself while her child was in the hospital. One child had otitis media and severe pyoderma on admission. There was good evidence, however, for maternal deprivation in this case, and a decided increase in weight occurred within a short period after admission.

Other points worthy of comment are as follows: There were two sets of brothers in this group. Twenty of the 26 patients were less than one year old and all but two were less than two years of age. The growth patterns in this group were variable. Although there was a significant gain in weight when the environmental circumstances were altered, in a two-year period of observation only one child reached a weight above the sixteenth percentile on the Iowa growth chart and a height within one standard deviation of the mean. After an initial spurt six infants and children gained steadily in height and weight, but both these dimensions remained abnormally small. Six children approached the sixteenth percentile in weight, but their height remained more than one standard deviation below the mean. Six of the children were under observation for too short a time to determine the nature of their growth pattern, although they did have an initial gain and did fit the criteria mentioned above. Two children, one with a severe emotional problem, gained very little, and the lines on the growth chart representing their rates of growth gradually fell away from the lines representing the sixteenth percentile. In four cases the height was not recorded often enough to establish a pattern. Skeletal age was assessed in nine children in this group, and in all of them osseous maturation was significantly retarded. It is interesting that only eight of this group of 26 were referred by physicians in private practice (Table 1).

Idiopathic Group

Ten children were included in this group. Four weighed less than 2,500 grams at birth and will be discussed below in the low birth weight group.

The period of follow-up ranged from three months to nearly five years. Seven were observed for a year or more. The shorter follow-ups were seven, five and three months. In this group, again, one child showed evidence of renal infection and subnormal function, one child had otitis media and diarrhea at the age of three weeks, and one had possible pyelonephritis when seen at the age of one month, although the diagnosis was not documented. One child vomited frequently and had persistent low fever, hypotonia and reduction or absence of deep tendon reflexes. The father was said to have had similar symptoms in the neonatal period, but recovered adequately. The child's physician indicated that the symptoms had disappeared after the second birthday and that he was in good health. A fifth child in this group had no symptoms and an excellent appetite on admission, but diarrhea developed after he entered the hospital.

The child with duplication of the renal pelvis subsequently gained weight adequately and reached the normal range in height and weight. The child with fever and hypotonia and the child with otitis media continued to gain regularly but had not reached normal height or weight. Follow-up examinations were not permitted in the case of the child with suspected kidney infection; but the father stated that at the age of five and a half months the child's weight was 17 pounds. The child in whom diarrhea developed shortly after admission to the hospital was observed for a period of three months only but seemed to be gaining adequately in height and weight. The diagnosis at the time of discharge was that of poor caloric intake, and this child may well have been affected by maternal deprivation. One child, who had a strong family history of allergic disease, was admitted with chronic cough, rhinorrhea and conjunctivitis and had several bouts of upper respiratory infections with otitis media during follow-up. He gained well, subsequently, into the normal range in both height and weight. In two patients with normal birth weight, bone age was measured and found to be within normal limits None of these children was considered to have significant mental retardation.

Unclassified Group

This group comprises seven children who were followed for relatively short periods and the cause of failure to thrive was not apparent. The ages when first seen ranged from eight days to one year. The follow-up period ranged from eight to fifty days. Four of the seven had vomiting, one had diarrhea, one fever, and one "persistent weakness." One had moderate mental retardation, unsuspected fractures on admission and a normal electroencephalogram. A sibling had similar problems. This may be an example of the "battered child syndrome." One child had mild arrested hydrocephalus, with possible mild motor retardation, at one year of age. One child was said to be premature even though the birth weight was 5 pounds, 14 ounces, and had a skull fracture at birth. Another child with a birth weight of 5 pounds following an apparently normal period of gestation, was admitted with complaints of vom-

TABLE 4.—*Information on 11 Patients with Low Birth Weight*

Patient	*Birth Weight* Lbs.	Oz.	*Gestation*	*Other Diseases Known or Suspected*
C.C.	3	12	"Premature"	Icthiosiforme erythroderma
D.G.	4	14	37 weeks	Interstitial pneumonia with atelectasis
J.C.	4	13	Not premature	Mental retardation, partial cleft palate
B.B.	5	0	"Overdue"	Mental retardation, spasticity
S.P.	3	3	"Premature"	Microcephaly with rubella syndrome
T.D.	4	14	35 weeks	Maternal deprivation
S.E.	5	0	Not premature	Suspected maternal deprivation
M.C.	5	1.5	Not premature	Poor speech development and myopia
E.R.	4	14	Term twin	Poor suck, mild retardation Twin sibling "twice as big"
M.B.	5	2	37 weeks	"Improper feeding"
P.K.	5	7	38 weeks	Duplication right renal collecting system Congenital hip dysplasia

iting and poor growth. Vomiting ceased on admission. It was found that the mother required careful instructions as to how to feed the child and the diagnosis on discharge was that of improper feeding. Two children had pneumonia, and one of the two also had hypotonic cerebral palsy and possibly mental retardation. None of the children in this group gained significantly in weight during the time in hospital. Over a more extended period of observation all the children were found to be gaining at subnormal rates. The child with moderate mental retardation and the child with cerebral palsy both had abnormal electroencephalograms. Bone age was measured in two and found to be within normal limits.

Low Birth Weight

Eleven children among the 78 in whom the birth weight was recorded weighed less than 2,500 grams at birth. For one of them the follow-up period was only 21 days. Five of the remaining ten had organic disease, one had evidence of maternal deprivation and four were also included in the idiopathic group. In all, six were said to have been born prematurely or after less than 40 weeks of gestation. There were four children whose birth weight was subnormal in whom no cause for growth retardation could be found. They were first seen at the ages of three, four, five and twelve months and were observed over periods of seven months to three years. The birth weights were between 4 pounds 4 ounces and 5 pounds 7 ounces. In one, duplication of the renal collecting system was noted on one side, but there was no evidence of infection or inadequate renal function. The other three had no significant disease. Three of the four had slight degrees of mental retardation. One child had considerable feeding difficulties. The twin of this child weighed 2 pounds more than his brother at birth and at the time of observation was close to the 84th percentile in weight, whereas the patient continued to have a subnormal growth rate. One child with no symptoms did reasonably well until the age of six months and then showed no significant weight gain between ages of six and twelve months. Pyelonephritis was said to have occurred at the age of nine months and speech development was poor. Two of the three children in this group whose bone age was measured, had retardation of osseous maturation.

Discussion

The grouping of the children into the categories designated above is arbitrary. It is of considerable interest that in one-third of the children the failure to grow adequately was apparently because of an inadequate environment at home. A decision as to whether maternal deprivation is the cause frequently cannot be made even after the most careful history from the parents. Accurate histories are often not obtainable in such cases because of unwillingness of the parents to disclose the truth or because of their ignorance of the existence of the problem. The cause of failure to grow in children with maternal deprivation is complex.[9,10] It is not clear whether growth failure results from insufficient intake of food, from decreased intestinal absorption or from more complex factors associated with disturbance of the social and emotional environment.[2,5,6,11,12] Provided the period of maternal deprivation is not prolonged, recovery can be expected with reasonable certainty. It is important for physicians to recognize this syndrome when it occurs so that adequate steps can be taken to prevent a return of the infant to the unfavorable environment.

This study focuses considerable emphasis on the association between mental retardation and poor

growth. There seem to be few children with mental retardation as the only cause of failure to grow; however, a considerable number of patients were mentally retarded. A child with mental retardation is also likely to be a candidate for caloric undernutrition and "maternal deprivation." Lack of response of the infant to his mother may result in inadequate maternal care. The exact roles of caloric undernutrition and organic brain damage in failure to grow are not understood.[7,8]

The frequent occurrence of organic disease in these children emphasizes the necessity for complete and careful physical examination of the child with failure to thrive. Persistent failure to grow requires that the child be admitted to a hospital for a complete and thorough investigation. At this time a careful search should be made for disease of any major organ such as stomach and intestines, kidneys, heart, lungs, pancreas, brain. Objective measurements of psychomotor development should be made. Such a thorough search is justified by the fact that an important disorder may not be evident except on extraordinary investigation.

It is noteworthy that the endocrine system is very rarely implicated in cases of failure to thrive. It may be that additional testing of some of the children in the idiopathic or unclassified groups will subsequently show that they have somatotropin deficiency, but it is unlikely that such cases will be more than a small fraction of the total number. Children with low birth weight falling into the category of primordial dwarfism or those born prematurely with feeding difficulties seem to make up an important segment of the children admitted with the diagnosis of failure to thrive.[3,7] Chronic infections and allergic involvement of the respiratory system are occasionally important.

REFERENCES

1. Ambuel, J. P., and Harris, B.: Failure to thrive. A study of failure to grow in height or weight, Ohio Med. J., 59:997, 1963.

2. Bakwin, H.: Emotional deprivation in infants, J. Pediat., 35:512, 1949.

3. Drillen, C. M.: A longitudinal study of the growth of prematurely and maturely born children. II. Physical Development Arch. Dis. Child., 33:423, 1958.

4. Falkner, F., Steigman, A. J., and Cruise, M. O.: The physical development of the premature infant. I. Some standards and certain relationships to caloric intake, J. Pediat., 60:895, 1962.

5. Fried, R., and Mayer, M. F.: Socio-economic factors in an institution, J. Pediat., 33:444, 1948.

6. Friend, G. E., and Bransky, E. R.: Physique and growth of schoolboys, Lancet 2:677, 1947.

7. Grossman, H., and Mosier, H. D.: Mechanisms of Regulation of Growth. Growth and Brain Defects, Proc. of the 40th Ross Conference on Pediat. Res., p. 56, 1961.

8. Kaplan, S. A.: Growth Disorders in Children and Adolescents, Charles C Thomas, Springfield, Illinois, 1964.

9. Patton, R. G., and Gardner, L. J.: Growth Failure in Maternal Deprivation, Charles C Thomas, Springfield, 1963.

10. Spitz, R. A., and Wolff, K.: Anaclitic Depression, The Psychoanal. Stud. Child., 2:313, 1946.

11. Talbot, N. B., Sobel, E. H., Burke, B. S., Lindemann, E., and Kaufman, S. B.: Dwarfism in healthy children: Its possible relation to emotional, nutritional and endocrine disturbances, New Eng. J. Med., 236:783, 1947.

12. Widdowson, E. M.: Mental contentment and physical growth, Lancet 1:1316, 1951.

13. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Charles C Thomas, Springfield, 1957, p. 8.



Drip Infusion Pyelography

Valuable Supplement to the Inconclusive Intravenous Pyelogram

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■ *By comparative studies of films, the superiority of infusion pyelography over conventional intravenous pyelography was confirmed.*

The technique is shown to be safe, even in the presence of uremia, diabetes, cardiovascular disease and advanced age.

It is well suited for outpatient use, and should reduce the need for retrograde uretero-pyelography to supplement the diagnostically inconclusive intravenous pyelogram.

ALTHOUGH THE ROLE of the excretory urogram as a diagnostic modality is unquestioned, the time-honored technique[4,7] has universally recognized limitations. It has been shown that 16 to 21 per cent of intravenous pyelograms by the conventional method are of inferior diagnostic quality.[1] Incomplete outline of distal calices and partially filled pelves are the most frequently encountered deficiencies. It is, moreover, unusual to see completely filled ureters on a single film.

The former uncomfortable alternative of reliance on an inadequate excretory urogram or of advising cystoscopy with catheterization of the ureters and retrograde pyelography can now in most instances be avoided. Accumulating studies strongly indicate that pyelograms of so-called "retrograde quality" are regularly obtainable by the continuous drip infusion technique.[2,3,5,6,8] Furthermore, this procedure lends itself easily to office practice. Most recently, the cumbersome chore of mixing and diluting the concentrated opaque medium with a suitable intravenous solution has been eliminated; a pre-packaged "ready-made" preparation has now been made available for investigational use.*

The following report describes the methods and the results in a series of 50 cases in a large Veterans Administration outpatient clinic physically separated by several miles from V.A. inpatient facilities. Admittance to hospital for supplemental retrograde study, formerly required after excretory urograms in 15 to 20 per cent of cases, is now rare.

Our interest in the continuous drip infusion method of pyelography was originally stimulated by the report of Schencker.[5] Subsequent reports[2,3,6,8] as well as our own studies have described the ancillary diagnostic dividends of nephrograms, nephrotomograms, cystograms and urethrograms. The diagnostic value and safety in cases of chronic renal failure are additionally worthy of note.

Methods of Investigation and Techniques

At the time our study was begun, the primary indication for resort to drip infusion pyelography was a previous inadequate or unsatisfactory pyelo-

From the Veterans Administration Outpatient Clinic, Los Angeles. Submitted 9 March 1967.

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*Hypaque Meglumine 30 per cent, Winthrop Laboratories, New York, N. Y.

gram. We now are using the method more frequently as an original procedure wherever a predictable situation warrants—that is, for comparison with previous retrograde studies, for patients with marginal uremia or for postsurgical evaluation and the like. In the beginning, our methods were similar to those described by others.[2,5] Routine bowel cleansing measures are employed. We do not use an enema, and we have no particular preference among the several purgatives available. No solid foods are allowed for 12 hours before the study, but fluids are not restricted.

For the first 25 cases in this study the contrast material was prepared by mixing a predetermined amount of 50 per cent diatrizoate sodium (1 ml per pound of body weight) with an equal quantity of 5 per cent dextrose in sterile distilled water in an ordinary sterile infusion bottle. The dosage was 2 ml of the resultant solution per pound of body weight. An 18 gauge needle was used and rapid unrestricted flow was permitted except when a slower rate seemed prudent because of cardiac disease or other limiting factors. The average time required for the infusion was 8 to 10 minutes. During the infusion and for 10 minutes after it was completed the patient was maintained in 5 degree Trendelenburg position (we are now not convinced that this is of any advantage). Exposures were made immediately upon completion of infusion and at 5-minute intervals thereafter up to 20 minutes (the last in erect posture). An excellent voiding cysto-urethrogram can then be made with slight oblique positioning. Many variations on the basic radiologic technique (for example, nephrotomography) may be employed as indicated.

Beginning with the 26th case in our series, a pre-packaged preparation of contrast medium was made available to us for investigative purposes. This consisted of an individually boxed glass bottle with sterile seal containing diatrizoate meglumine 30 per cent* together with a sterile disposable injection tubing set made of plastic, with suitable adapters for connection with an infusion bottle. (There were also catheter connections for retrograde cysto-urethrography.) These sets contained either 300 or 500 ml of the contrast material. The difference in amount afforded us opportunity to compare two dosage levels of this agent in a random fashion by leaving entirely to chance the selection of a 300 ml or a 500 ml bottle, and employing a dose schedule relative to the selection of the bottle in the following manner: If a 300 ml container was selected, that entire dose was administered; alternatively, when a 500 ml bottle was chosen a dose calculated at 2 ml per pound of body weight was used. We thus were able to assess the potential difference between a fixed, safe (though potentially high) dose and a dose estimated on the basis of body weight, as to advantage or detriment.

*Hypaque Meglumine 30 per cent, Winthrop Laboratories, New York, N.Y.

Results

Included in this report are the findings obtained in 50 consecutive cases in which infusion pyelography was done. All pertinent information was recorded. Where there was confirmed previous allergic reaction to opaque media, no injection was attempted. Where reasonable doubt existed, 2 ml was injected intravenously and a 3-minute period of observation followed. If there was no untoward effect, infusion was continued.

No reaction occurred which could be evaluated as more than of mild degree. Occasionally we noted mild nausea and "flushed feeling" within 20 to 60 seconds after infusion was begun. In each



Figure 1.—In a 41-year-old man with anomalous complete duplication of left ureter, the distal ureteral segments are fully outlined by the drip infusion technique.

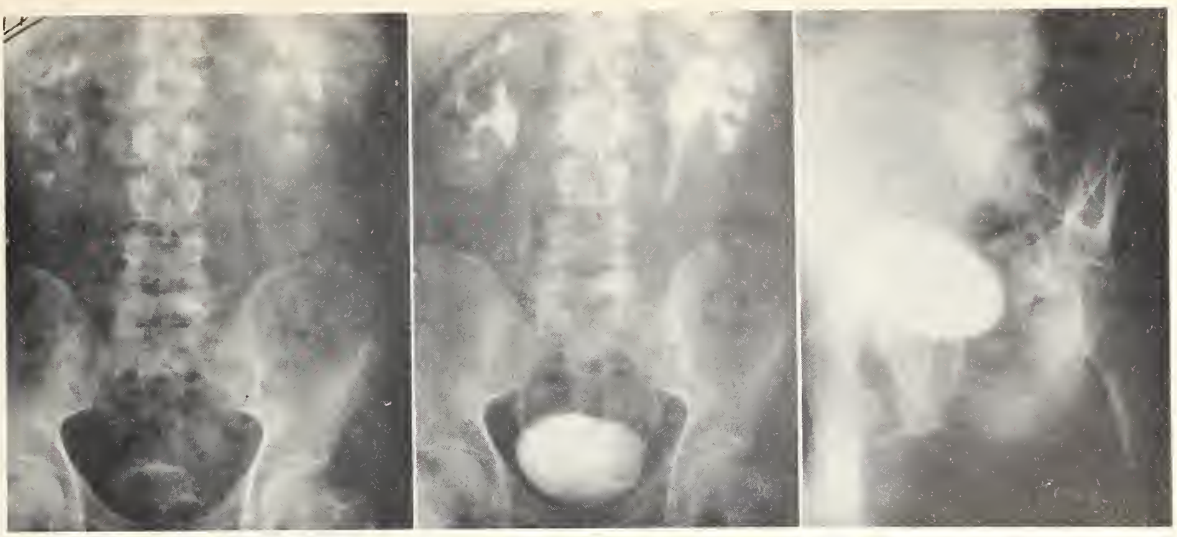


Figure 2.—*Left,* routine intravenous pyleogram of 41-year-old man with ancient left nephrolithotomy and residual hydronephrosis and chronic right pyelonephritis. *Center,* drip infusion pyelogram. *Right,* voiding cysto-urethrogram. (The best film of each series is shown.)

instance, slowing of the intravenous drip rate for 20 to 30 seconds resulted in quick relief of these symptoms. We were then able to resume free-flow speed without recurrence. In two patients, the appearance of isolated small areas of hives caused us to discontinue infusion after 200 ml was given; yet in each of these instances the films were of good diagnostic quality.

All films were evaluated by radiologist and urologist jointly. In 20 instances were routine pyelography had previously been done, comparative evaluations were made. Grading on a scale of one to four, representing poor to excellent, was carried out separately for calices, pelves, ureters and bladder. Results are tabulated in Table 1.

Comment

The quality of anatomic delineation, density of contrast medium and, therefore, of diagnostic accuracy is significantly superior when infusion pyelography is employed. This applies from renal cortex to the distal urethra.

We have found the safety of infusion pyelography quite comparable to that of routine intravenous pyelography, and we have used it in the elderly, in patients with diabetes and uremia and in some cases in patients with known cardiovascular disease. No significant differences between 300 ml doses and doses related to body weight were noted.

In our opinion, increased use of infusion pyelography will significantly reduce the indications for retrograde ureteropyelography. We of course have no intention of degrading the value and importance of either observation cystoscopy or differential renal studies where these are indicated.

In addition, since infusion pyelography is well suited for outpatient use, the patient need not be put in hospital for that purpose alone. This has proved of particular value in a large outpatient

TABLE 1.—*Comparative Diagnostic Quality of Films Obtained in Infusion Pyelography Studies—Mean Values in 20 Cases, Rated on a Scale of 1 to 4**

	Conventional Intravenous Pyelogram (Mean Values)				*Drip Infusion Pyelogram (Mean Values)*			
	Time from Beginning of Infusion							
Organs Visualized	*5 min. Grade*	*10 min. Grade*	*15 min. Grade*	*20 min. Grade*	*5 min. Grade*	*10 min. Grade*	*15 min. Grade*	*20 min. Grade*
Calices	1.60	1.95	2.10	1.85	3.30	3.35	3.45	3.45
Pelves	1.55	1.85	2.25	1.90	3.35	3.35	3.40	3.40
Ureters	1.10	1.45	1.65	1.70	3.35	3.40	3.40	3.40
Bladder	1.30	1.40	1.65	1.60	3.30	3.30	3.50	3.50

*4—excellent; 3—good; 2—fair; 1—poor

clinic of the Veterans Administration, and this advantage might be equally applicable in private practice.

REFERENCES

1. Hartley, W.: Infusion urography, Clin. Radiol., 17:237-41, July 1966.

2. Henson, P. E., and Boyarsky, S.: Constant infusion excretory urography, J. Urol., 95:814-17, June 1966.

3. Neal, M. P., Howell, T. R., and Lester, R. G.: Contrast infusion nephropyelography, JAMA, 193:1017-20, Sept. 1965.

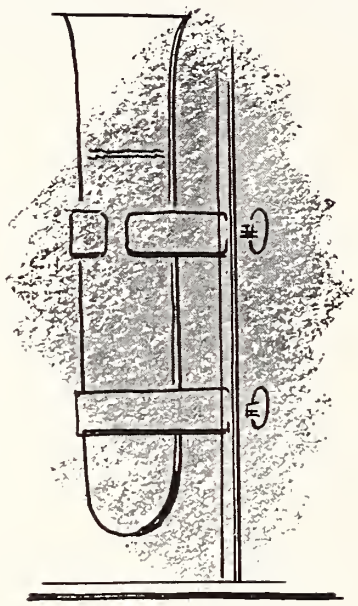
4. Rowntree, L. G., Osborne, C. D., Sutherland, C. G., and Scholl, A. J.: Roentgenography of the genito-urinary tract during excretion of sodium iodide, JAMA, 80:368-73, 1923.

5. Schencker, B.: Drip infusion pyelography, Radiol., 83:12-31, 1964.

6. Schencker, B., Marcure, R., and Moody, D.: Simplified nephrotomography, Amer. J. Roentgenol., 95:283-89, Oct. 1965.

7. Swick, M.: I.V. urography by sodium salt of 5-1-2-pyridon acetic acid, JAMA, 95:1403-12, 1930.

8. Whitesel, J., and Heller, E.: Intensification of excretory urogram by continuous infusion of contrast material, J. Urol., 92:224-29, Sept. 1964.



Effects of Automation on Laboratory Diagnosis

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■ *There are four primary effects of laboratory automation on the practice of medicine: The range of laboratory support is being greatly extended to both diagnosis and guidance of therapeutic management; the new feasibility of multiphasic periodic health evaluation promises effective health and manpower conservation in the future; and substantially lowered unit cost for laboratory analysis will permit more extensive use of comprehensive laboratory medicine in everyday practice. There is, however, a real and growing danger of naive acceptance of and overconfidence in the reliability and accuracy of automated analysis and computer processing without critical evaluation. Erroneous results can jeopardize the patient's welfare. Every physician has the responsibility to obtain proof of accuracy and reliability from the laboratories which serve his patients.*

THE USE OF automation in medical laboratory processes will be guided by the emerging patterns of medical practice of the future. An enlightened American society is demanding better medicine for everyone at lower cost. Industry is responding by a growing tendency to provide total medical care for employees through industrial health programs and private insurance coverage for sickness. Congress is responding by enacting federal legislation to provide "medicare", regional medical centers, diagnostic facilities for heart disease, cancer and stroke and "preventicare." The medical profession is responding by organization of large group practices, consolidated metropolitan hospital centers and regional centralized medical laboratories.

The immediate effect on laboratory medicine is great. Automation has the capacity to provide multiphasic test profiles for initial evaluation of the patient's problem. Use of such surveys as a part of the routine complete examination is uncovering unsuspected abnormalities. Application of medical research knowledge in the form of new tests is increasing. Larger and more complex batteries of tests are needed for daily evaluation of the patient's progress and guidance of therapeutic management. This is particularly important during intensive chemotherapy. Thus, laboratory medicine is rapidly assuming a central and indispensable role in all phases of health evaluation and medical management. Although the growth rate of laboratory work in larger hospitals has been averaging 15 per cent per year for the past decade, recent acceleration in public and private medical programs already is causing a sharp increase in demand for laboratory tests and there is no reason to expect a leveling-off in the foreseeable future. The existing shortage of manpower and space resources for the laboratory is becoming acute. Immediate remedy is needed.

Clinical pathologists throughout the nation are meeting this challenge by intensive programs for

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development of automated, mass production methods along with improved accuracy, reliability and lower cost. Laboratory medicine of the future must make available (at acceptable cost) complete laboratory service, including highly specialized knowledge of pathologic physiology and chemical abnormalities, provided by competent laboratory physicians and scientists. An on-site laboratory intimately integrated with the function of the patient care facility, whether it be a hospital or a group practice clinic, and staffed by clinical pathologists can provide immediate laboratory service and collaborative assistance in the interpretation and correlation of complex specialized laboratory data. An automated, computer-assisted central laboratory for economic mass production of quality controlled routine tests and special and difficult procedures can serve a geographic group of pathologists in their hospitals and clinics.[3]

The central or regional laboratory can be implemented by sophisticated automatic instrumentation, high speed computer processing and error checking and an advanced program of quality control to assure continuous reliability. Test results can be mass-produced with improved accuracy and reliability. Carefully designed computer programs will compare new test results with previous results on the same patient and report any deviation or abnormality as compared with the patient's normal ranges. Complex profiles of multiple tests can be correlated and expressed in integrated fashion most useful to the patient's physician. There are beginnings of programs to provide high speed computations of physical and chemical data to evaluate complex physiological balances as they exist in the individual patient and to compute the necessary therapeutic measures to return the bodily processes to normal. Such guides to medical management will greatly extend the power of each physician to arrive at the best decisions in difficult problems, to begin specific therapy earlier and to shorten hospital stay.

In the function of periodic health evaluation a large part of the initial examination routine can be assumed by appropriate combinations of multiphasic laboratory screening tests.[1] Automation makes this economically feasible and thus can spare a physician much of the tedious and time-consuming, routine physical examination. He will have a comprehensive laboratory report to help guide the further examination of the patient. It would be most useful to have for each patient an individual base-line chemical and physiologic profile and a record of recent deviations from his base-line; but, although this is technically feasible, the requirement of obtaining large specimens of blood by venipuncture each week for 10 to 12 weeks to establish the basic profile is impractical. Soon, however, it will be possible to do this with little inconvenience to the subjects by ultramicro methods on capillary (fingertip) blood. After establishing the base-line profile for each person, subsequent and significant changes discovered in the course of periodic examinations can be evaluated by comparison with the stored profile record and reported promptly to the physician for appropriate medical action[2] (Chart 1).

These advances impose an ever greater responsibility on our profession, on both the patient's physician and his colleagues in the laboratory. Serious hazards to the patient's health from misinformation are more likely with automation unless careless use is avoided. Paradoxically, the very potential of automation for more accurate, reliable and extensive laboratory testing generates a tendency to overconfidence, to uncritical acceptance of results because they are from an "automated laboratory" and to relaxation of the traditional surveillance of physicians for the protection of patients. Naive acceptance of the exaggerated claims of some equipment and computer manufacturers and adoption of their analytical systems without critical evaluation, calibration and continuing vigilance through effective quality control measures will permit test results which are so varied and unreliable as to be gravely misleading. Twenty-five to 75 per cent technical variability can be experienced in the use of insufficiently controlled "automated" equipment.

When large numbers of specimens are automatically prepared and analyzed, and the results printed out of a computer system, there is the hazard of misidentification and neglect of cross-checking of patient's name and specimen number. Recently, and quite inadvertently, two specimens of blood from the same patient, each labelled correctly, were sent to a large "quality controlled" automated laboratory, each submitted for a different "test package." But the two "test packages" that were ordered happened to contain one common test. Both specimens were analyzed the same day and the two reports were delivered in the *same* envelope. Nevertheless, the two results for the one test in common were widely disparate,

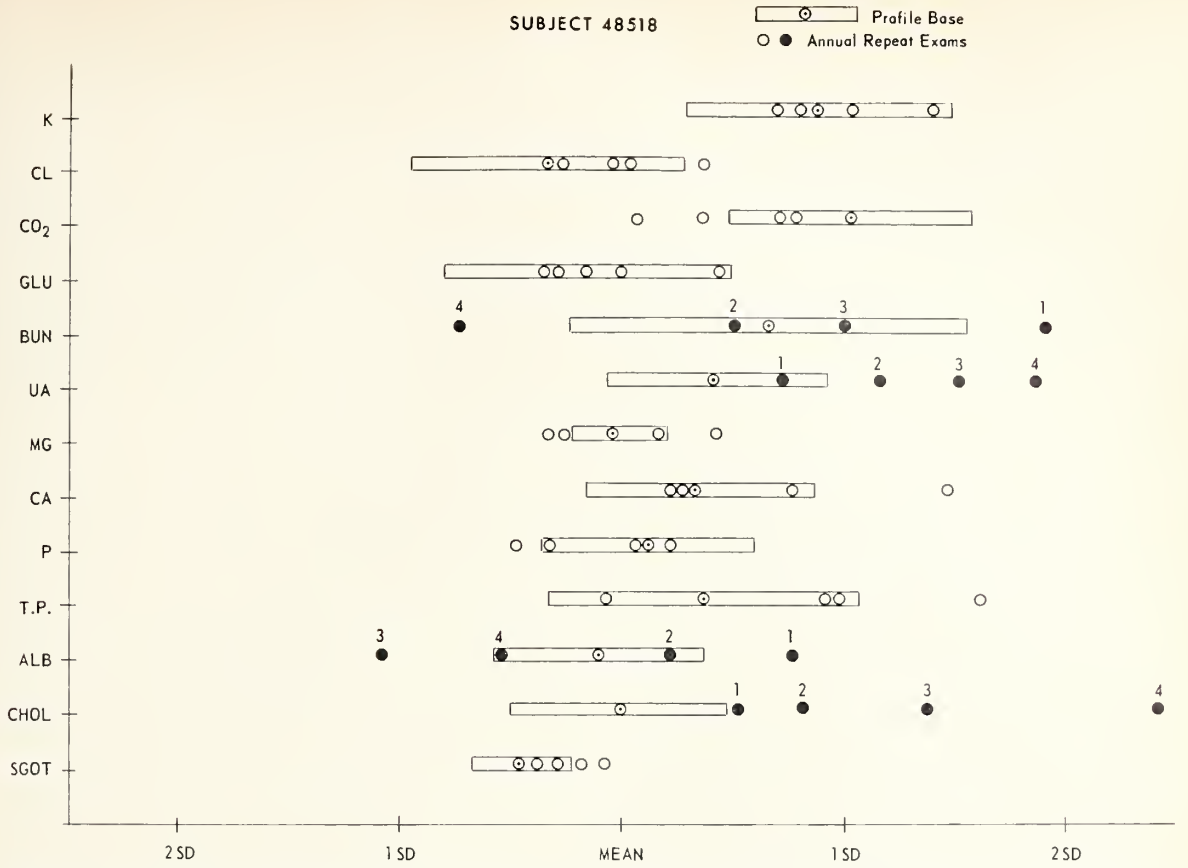


Chart 1. A hypothetical example of changes in a person's profile determined by periodic repetition of laboratory tests. The open circles represent new results obtained at yearly intervals and within expected normal deviation. The solid dots represent subsequent test results which reveal a pathologic trend in one direction although still within the range of the population extremes. Such information should alert the physician to seek an explanation or cause for the shift.

indicating unacceptable reproducibility and breakdown or lack of adequate quality control. Grossly inaccurate analytical results and unreliability can mean danger of being misled, direct hazard to the patient's health and medical management, and unwarranted expense.

Multiphasic screening tests with 25 to 100 per cent variability are meaningless in defining profiles or detecting abnormalities and can lead to either falsely normal or abnormal interpretations. Thus, automation does not assure reliability. Computers can make and perpetuate errors. Worse, such results can encourage a false sense of security.

It behooves the physician to satisfy himself that the laboratory on which he depends is reliable. Only the patient's physician can assure reliable laboratory service. He is obligated to require documented evidence of reliability from the laboratory he selects. Periodically he should submit duplicate samples on different days to compare the results.

Accreditation of a laboratory, regardless of the professional stature of the accrediting agency, cannot guarantee continuing reliability. Acceptable accuracy and reliability are matters of unrelenting daily vigilance on the part of the laboratory physicians and scientists.

Because the clinical pathologist is a physician, he is acutely aware of the medical implication of false or inaccurate analytical results and therefore is motivated and competent to exercise rigorous quality control. Since effective quality control is expensive, the most reliable services will not be the lowest in cost, and in the long run cheaper services will be the most costly to the patient.

1. Collen, M. F.: Periodic health examination using an automated multitest laboratory, JAMA, 195:830-833, 1966.

2. Williams, G. Z.: Clinical pathology tomorrow, Am. J. Clin. Path., 37:121-124, Feb. 1962.

3. Williams, G. Z., Breckenridge, R., Derman, H., Hartwell, R. M., Hagebusch, O., and Straumfjord, J.: Report of Ad Hoc Committee on Regionalization of Laboratories, Bull. Coll. Amer. Path., 21:108, Apr. 1967.

GOVERNMENT AND MEDICINE

Regional Medical Programs

ROGER O. EGEBERG, M.D., *Los Angeles*

IN THE PAST decade or two, the acceleration in medical knowledge has reached such a pace that the total has doubled since 1938 and will probably double again in the next 15 or 20 years. In light of this rapid expansion of what physicians must know if they are to give good medical care to patients, the continuing education of physicians and the allied health professionals has become as necessary as their initial undergraduate teaching and training. More, the sociologic aspects of distributing the benefits of these advances in medical knowledge demand more and more attention.

It is toward these two ends—distribution of care and continuing education—that Public Law 89-239, the Regional Medical Programs for Heart Disease, Cancer and Stroke, is primarily directed. This program, resulting from the deliberations and recommendations of the President's Commission on Heart, Cancer and Stroke (the DeBakey Committee) has been much maligned by practitioners and educators alike, but one can no longer avoid the realization that this great effort is sorely needed, and without such governmental stimulation and help it would probably be several decades off, and even then evolve piecemeal.

In the years immediately after World War II most attention had centered on the mushrooming of the national research effort in medical science. The National Institutes of Health of course played a vital part in this process, with a strong stimulus from Senator Lister Hill and the late Representative John Fogarty. The medical schools, as an important arm of research, very quickly had to come to grips with the realities of a new world of governmental relations.

During much of the same period, those concerned with health services had to consider and deal with federal participation in hospital construction through cost sharing. Finally, at the point where public interest in the problem was brought to the highest pitch, the medicine-and-government relationship was extended, by the passage of Public Law 89-97 (Medicare), to include a measure of payment for services to patients.

We all remember well the keen debate in Congress and the strong feelings generally that were associated with the development of all these programs. This intense interest caused some reexamination of trends in the broad field of health and affected people in government as well as those in medicine.

Public Law 89-239 is a product of that reexamination. It represents a conscious effort to see that the fruits of two decades of medical research be made available to all, with particular concern for those who were the furthest from centers of evolving knowledge. Early in the evolution of the law descriptive terms such as "centers of excellence" raised some alarm in that they seemed to imply a threat of governmental interference with the established patterns of patient-physician relationship and referral. These were later replaced by descriptions placing the emphasis on support for the farthest periphery—for the grassroots. Congress was particularly anxious that those grassroots be reached, be they growing on the concrete pavements of large metropolitan areas or in communities on the edge of a desert, or even in places where grass is supposed to grow. The law addressed itself to the medical establishment, includ-

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ing the Surgeon General and his representatives as well as the university medical centers, the other major medical centers, the professional organizations and the health establishment as a whole. It asked that we turn to account what we now know, and now have, and enhance its effectiveness with cooperative effort, backed by relatively small appropriations of federal money.

New construction, as such, was not a part of this program. Congress felt that such laws as the Hill-Harris legislation discharged the federal responsibility in this area—Regional Medical Programs can only finance a certain amount of renovation in its advanced, or operational, phase.

Similarly, payment for patient services is not a part of this program. Services to patients may only be supported by Regional Medical Programs where they serve a demonstration purpose in pilot projects.

The bulk of support is given first to a planning effort within regions designated as such by the Surgeon General. The planning, on the basis of appropriate data gathering, is to sketch out ways in which existing resources, facilities, manpower and organizations can be brought voluntarily into cooperative arrangements which can make the most advanced of medical capability in heart disease, cancer and stroke available to the patient and the physician of his choice.

The nature of these cooperative relationships is not specified. Each region seeks its own route. In California, we have been doing just that with a state-wide program that should have cohesiveness, cooperation and coordination. Here we have formed the California Committee on Regional Medical Programs. This Committee is made up of representatives from the medical schools, the schools of public health, the California Medical Association, the California Hospital Association, the Heart Association, the California Division of the American Cancer Society, and the State Department of Public Health. Eight representatives best identified as consumers' representatives serve as advisory members to the CCRMP. The 19 CCRMP members with the eight public members constitute the Regional Advisory Committee whose purpose is to solve questions of overlap of interest or area, to see that no areas are left out, to pass on the validity of the various programs suggested, to encourage programs in general, to act as a cohesive force in what might be considered a federation of purveyors and consumers. Within this structure, preliminary geographic delineation of eight realms of influence, each containing a medical school, has been suggested. These will be further worked out. Grants have been requested, coordinators of the programs have been appointed and efforts are being made to involve hospital staffs in the programs which as a matter of course emphasize a new and presumably strengthened venture in the old field of continuing medical education. Also high on the priority lists in most regions are demonstrations and training projects in advanced techniques—for example in the setting up of coronary care units. Most regions, ours included, are taking a hard look at such problems as storage and retrieval of medical reference material, extension and strengthening of medical library networks, and transportation factors where they may affect delivery of vital services for heart disease, cancer and stroke.

Activities of the CCRMP

Among the funds allocated from the first supplementary grant awarded last spring were modest sums to the California Medical Association and the California Hospital Association. But modest through they were in finances, the two projects helped conspicuously in putting the base structure of the Regional Medical Program on a firm footing.

The CMA is refining a survey questionnaire to seek information from a representative sample of practicing California physicians on continuing education. Such questions as "What courses of postgraduate instruction do you take" and "What would you like to see offered that is not available" are at the heart of these surveys. This activity by the CMA was preceded by and now is concurrent with strong and continuing support given by the Association to the concept of regional medical programs. The CMA Council has endorsed the formation in each component county society of a regional medical program committee whose function is to help each local community obtain professional guidance in the development of its program. Several county societies have created these RMP committees, and they are actively at work.

The California Hospital Association project was also intended to stimulate interest throughout the community of 600 or more hospitals in the state. Informational meetings have been held by the CHA in widely scattered communities, and among those attending from the hospital family

have been hospital administrators, chiefs of medical staff, directors of medical education and chairmen of boards of trustees. A medical school representative and a staff member of the California Committee on Regional Medical Programs have shared speaking duties at these meetings with CHA representatives.

The bulk of the Committee's activities has been centered, so far, in the medical schools of the state. Recruiting for top level staff has, for the most part, proceeded slowly. Nevertheless, each area has generated a large and variegated volume of response, interest and desire to become involved in regional medical programs—even among the far reaches of the medical school's geographic planning effort.

At the same time, the CCRMP established a Committee of Staff Consultants, composed largely of area coordinators and deputies to the members of the full CCRMP. The Staff Consultants in turn created four subcommittees to guide activities vital to each of the areas.

A Subcommittee on Communications has helped make the nature of RMP better known throughout the health community in California. It was aided in this by brochure material distributed by the California Medical Association. Further informational material is being prepared.

A Program Development Subcommittee has given counsel to the CCRMP on the problems involved in setting up RMP where it does not now exist.

An Evaluation Subcommittee has taken on the planning for one of the most crucial jobs in the program, finding answers to questions such as: What have been the consequences of RMP? What will physicians retain from continuing medical education? Will such programs reach new areas? What in the long run will be the effects—if any are measurable—on mortality and morbidity?

Finally, a Data Needs Subcommittee has grappled with the acquisition of hard facts needed to prepare the way for operational projects. Each area has data needs. These are coordinated by the subcommittee. Overlaps and duplications are avoided, where possible. Gaps in the data picture are filled. And five planning studies which go beyond the basic data on population, mortality and transportation have been launched.

One study is constructing an inventory of teaching facilities for manpower in the allied health fields. This is basic to training programs which may become operational. Another will survey patient geographic origins, based on hospital discharge forms, throughout the state. A third will interview a sample of physicians to obtain their views on referral patterns in heart disease, cancer and stroke. A fourth will make a new approach to review and analysis of morbidity data, based on county medical society review mechanisms. And, last, a look is being taken at the problem of registries and the possibilities of follow-up inherent in them for the categorical fields other than cancer.

All of this activity is pointing toward operational projects in the near future. The operational program, with the continued cooperation of all components of the health professions, points toward a new kind of regional relationship between medicine and government.

This short description of the Regional Medical Programs in California ends on an upbeat since the programs are still in the making, still in the shaping.



A Conference at Chandler

AN EDITORIAL, "The Shaping of Medicine's Future," referring to The Western Regional Conference on Future Directions and Decisions in Medical Care*, appeared in the November issue of CALIFORNIA MEDICINE. The Conference, which was held in Chandler, Arizona, November 10 to 12 under the auspices of the California Medical Education and Research Foundation, was devoted to a discussion of Public Law 89-479 — the "Comprehensive Health Planning and Public Services Amendments of 1966."

Over 200 physicians, representing the medical leadership of 14 western state medical associations, including Alaska and Hawaii, met three days for the primary purpose of discussing medicine's obligations and responsibilities under the comprehensive health planning legislation. The Conference was not held as a direct response to Public Law 89-749, since the motivation for it had begun almost two years ago in recognition of a need to explore some of the problems and issues confronting the medical profession. The passage of this legislation, however, brought into focus some of the immediate and long-range issues which the organized medical profession has to face if it is to deal realistically with the problems ahead. The meeting therefore concentrated on Public Law 89-749 which contains within it the elements related to personal and environmental health services in which the medical profession has been interested for many years.

The goals to which the Conference addressed itself were:

1. To assist in creating a better understanding of the issues which are to be faced and the means whereby various problems can be analyzed and evaluated;

2. To focus on the need for physician and medical society immersion and involvement in the total health planning and decision-making process;

3. To encourage continuing self-evaluation and re-evaluation of professional and community efforts in assessing outcomes of activities undertaken and in charting new goals; and

4. To stimulate participants to impart to physicians in their communities the information derived from the conference, and thereby serve as catalysts in the achievement of mutually acceptable community health goals.

The Conference participants were also given a series of six questions to answer which were then incorporated in six workshop summaries representing the consensus of the discussions. Although there was a wide range of opinion expressed, the major chord struck in all workshop summaries was that medical leadership, involvement and participation were not only important but were essential if the provisions of the law are to be implemented in a manner which will be beneficial to the health of the public and in the best interests of the physicians and of the communities in which they serve. It was recognized by several speakers that not only was such activity a continuation and outgrowth of medicine's previous and current efforts, but that it gave added force and meaning to the medical profession's involvement in the conclusions and recommendations reached by the National Commission on Community Health Services and as they are contained in the publication, "Health is a Community Affair."

In speaking to the subject of "The Goals and Objectives of the Medical Profession," Dr. Dwight L. Wilbur, President-Elect of the American Medical Association, shared with the audience an 11-point statement of purposes and responsibilities of the AMA which were subsequently contained in Report I of the AMA Board of Trustees and adopted by the AMA House of Delegates at the Houston meeting. He noted that such elements represented no new departure from the historical role played by organized medicine, but rather

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elaborated on those policies and objectives which define and further refine medicine's role in society. These objectives, he felt, were in consonance and compatible with the nature of medicine's response to and involvement in comprehensive health planning activities. The significance of Dr. Wilbur's presentation and the 11 points he presented lies in the fact that they represent the major components of the areas of physician involvement under Public Law 89-749. They are as follows:

The Purposes and Responsibilities of the American Medical Association

It is the responsibility of the American Medical Association, as the representative of the American medical profession, to foster the advancement of medical science and the health of the American people.

Its purposes are to meet this responsibility through the following means:

(1) By encouraging the further development of medical knowledge, skills, techniques and drugs; and by maintaining the highest standards of practice and health care.

(2) By creating incentives to attract increasing numbers of capable people into medicine and the other health-care professions.

(3) By advancing and expanding the education of physicians and other groups in the health-care field.

(4) By motivating skilled physicians who have the art of teaching to apply themselves to developing new generations of excellent practitioners.

(5) By fostering programs that will encourage medical and health personnel to serve voluntarily in the areas of need for medical care.

(6) By developing techniques and practices that will moderate the costs of good medical care and health care.

(7) By seeking out and fostering means of making all health-care facilities—physicians' offices, hospitals, laboratories, clinics and others—as efficient and economical as good medical practice and attention to human values will permit.

(8) By combining the utilization of the latest knowledge for prevention and treatment with the vital healing force of the physician's personal knowledge of and devotion to his patient.

(9) By maintaining the impetus of dedicated men and women in providing excellent health care by preserving the incentives and effectiveness of unshackled medical practice.

(10) By maintaining the highest level of ethics and professional standards among all members of the medical profession.

(11) By continuing to provide leadership and guidance to the medical profession of the world in meeting the health needs of changing populations.

Additional Conference Notes

A number of misgivings were expressed with regard to the role of government and its potential for interfering with the practice of medicine, but several speakers noted that Section 2(a) of P.L. 89-749 specifically states that the attainment of comprehensive health services of high quality for every person shall be accomplished "without interference with existing patterns of private professional practice of medicine, dentistry and related healing arts." The provision within the Law for the availability of grants to support comprehensive health planning activities on the local level was also viewed with some suspicion by some participants, but the consensus appeared to be that such monies were, in fact, taxpayers' contributions and therefore could and should legitimately be sought in order to assist activities in which the medical profession would be involved.

Dr. Gerald Besson, President of Santa Clara County Medical Society, succinctly summarized some of his philosophy with which there appeared to be considerable agreement:

* * *

"We are now wed to the Federal Government and, like any marriage, it will be whatever we jointly make of it, providing we communicate, and, providing we understand each other," he said.

"So, I have a new set of premises and these basic premises are as follows:

(1) Medicine is now subject to public policy.

(2) Public policy now states that health is a right.

(3) Public policy knows that an unfettered profession can provide the best quality of care, and, at this point at any rate, tends to protect the profession's integrity.

(4) Public policy, therefore, looks to the profession for leadership and guidance in the areas of its expertise and we must supply it.

(5) This now creates a new role for the profession. We are now responsible for the public health, in addition to the health of our individual patients.

(6) This new responsibility demands our solution or at least our creative thinking, on problems of costs, manpower, rational planning, social inequities and the often archaic organization of our current health care systems.

(7) In order for the profession to effectively perform in this role, it must change its organizational character to work with federal resource assistance and seek pluralistic solutions to these problems."

* * *

Among the several recommendations of the Conference was the call for involvement and participation in comprehensive health planning activities, the convening of similar regional conferences under the sponsorship of the AMA, the preparation by the AMA of a statement of basic principles underlying comprehensive health planning activities, and a study on the effect of professional liability on new manpower development.

The primary objective of the California Medical Education and Research Foundation was to bring together leaders of medicine in the western region to create an "awareness of some of the challenges, responsibilities and objectives confronting the medical and allied health professions on all community levels with the passage of Public Law 89-749." To Doctor John G. Morrison, President of CMERF and to Doctor James C. MacLaggan, immediate past president and one of the primary movers of the Conference, this objective was fully realized as evidenced by the nature of the discussions and the responses of the participants of this historic meeting.

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CASE REPORTS

Gynecomastia, Hypospermatogenesis and a Large Y Chromosome in a Man

K. W. DUMARS, JR., M.D.,
AND C. E. FISHER, M.D.,
Colorado Springs, Colorado

UNTIL THE RECENTLY described YY Syndrome,[1,3,7,8,9] characterized by the tall, mentally retarded, and institutionalized or criminal male, the Y chromosome abnormalities were clinically unrecognized.

This report concerns a young adult male with gynecomastia and hypospermatogenesis who has an elongated Y chromosome.

Report of a Case

A 20-year-old male college student was in good health until January 1961, when he noted a slow and painless breast enlargement, greater on the left side than the right. The breast development became a severe emotional problem, for which he sought medical treatment.

The patient described normal male libido.

On physical examination in March 1964 the patient was observed to be well developed, well nourished and of normal proportions. Breast enlargement with palpable glandular tissue was noted on both sides. The nipples were flat. Genitalia and hair distribution were normal.

Blood cell counts and results of urinalysis were within normal limits. X-ray films of the skull and intravenous urograms showed no abnormality. Reaction to a frog test for pregnancy was negative. Results of a 24-hour specimen of urine (1160 ml) were as follows:

Pregnanediol, 2.3 mg; pituitary gonadotropin (follicle stimulating hormone) less than 6 units; 17 ketosteroids, 12.8 mg in 23 hours; 17 ketogenic steroids 17.4 mg in 14 hours.

Microscopic examination of a testicular biopsy specimen showed pronounced disorganization of spermatogenesis and hypospermatogenesis.

The patient was admitted to the hospital where simple mastectomy was performed, approximately 200 gm of tissue being removed from each breast. Microscopic examination of the operative specimens showed increased collagenous connective tissue surrounding nests of increased mammary ducts. The ducts were lined by several layers of epithelial cells which were proliferating focally. It was the pathologist's impression that the slight ductal hyperplasia was consistent with a diagnosis of gynecomastia.

At this time, cytogenetic studies were completed. A buccal smear revealed 100 per cent chromatin-negative cells.

Preparations of the patient's chromosomes were obtained from peripheral blood. The leukocytes were cultured in Ham's F10 media. After three days, the cells were harvested, treated with colchicine, placed in hypotonic solution, fixed and stained. The figures were analyzed as described by Patau.[6] Thirty-five figures were studied; 30 of them had 46 chromosomes; five had a non-modal number, but an inconstant pattern, and were believed to be non-modal due to broken cells. An unusually large acrocentric chromosome (see Figure 1) was present in all figures.

Discussion

The mass of the large Y chromosomes found in

Submitted 26 May 1967.
Reprint requests to: Department of Pediatrics, University of California, College of Medicine, 1721 Griffin Avenue, Los Angeles 90031 (Dr. Dumars).

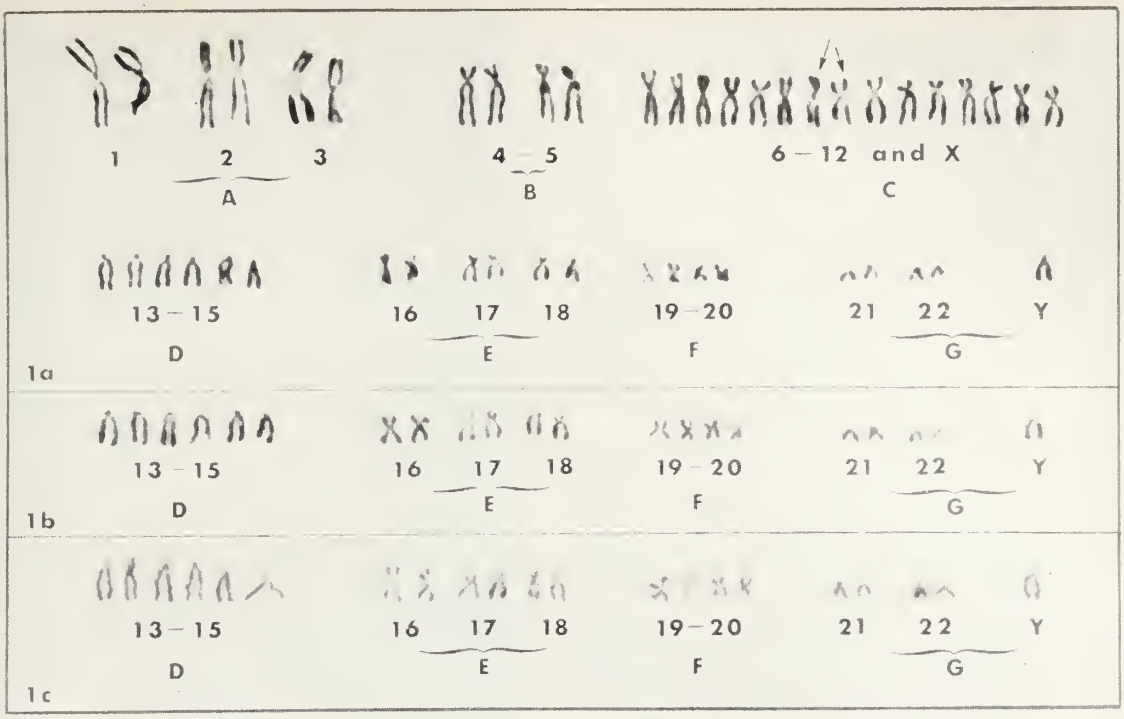


Figure 1.—Karyotype from three mitotic figures, 1a, 1b, and 1c, the latter two figures including only groups D, E, F, and G. Each figure demonstrates the elongated "Y" chromosome. (Note the C′ in figure 1a marked by arrows).

this patient approached the mass of one of the D chromosomes; however, six D chromosomes were present. In addition, all chromosomes of the E, F, and G groups were present and normal.

We and other investigators[2,4,5,6,10] have observed that there is a decided variation from patient to patient in the size of the Y chromosome. In the present case the Y chromosomes were the largest we have seen. Upon determining the Y_2, Y_f and contraction indices (see Table 1) in our patient, we found indices to equal those cited by Cohen and coworkers[4] in their group of patients with elongated Y chromosomes. This is cited not as an indication of abnormality, but only as a means of placing the size of this Y chromosome in perspective.

Unfortunately, the true parents of this young man are not known. He was adopted by his present parents during his infancy. The large acrocentric chromosome must represent more than an elongated Y chromosome. If this were an elongated Y, we could anticipate witnessing the adherence of "stickiness" of the long arms of the Y; this was found infrequently in the figures analyzed. It is tantalizing to speculate that a translocated segment of another chromosome, possibly the X

TABLE 1.—*Chromosome Indexes in Present Case Compared with Those Reported by Cohen and Coworkers*[6]

Variation in Y Chromosome Length		*Y_f Index** Mean	*Y_f Index** SD	*Y_2 Index** Mean	*Y_2 Index** SD	*Contraction** Index Mean	*Contraction** Index SD
Racial groups	Indian	0.88	0.11	0.29	0.05	0.20	0.06
	Japanese	1.00	0.15	0.33	0.06	0.20	0.05
	Negro	0.92	0.09	0.30	0.04	0.20	0.05
	Jew	0.94	0.10	0.29	0.05	0.18	0.07
	Non-Jew	0.86	0.09	0.27	0.04	0.19	0.06
	Present case	1.28	0.17	0.31	0.03	0.16	0.04

*Y Index = Total length of Y chromosomes / Average total length of "Standard Chromosome," i.e., 2,F

**Contraction Index = Average width of short arm #2 / Average length of short arm #2

chromosome, is present in the Y; however, no donor site is visible. Admittedly, the extra segment could be an autosomal fragment which influences secondary sex characteristics. However, if this were a translocated segment from an autosome producing an unbalanced translocation, more profound and diverse manifestations would be anticipated. The possibility of a Y isochromosome must be entertained, but the morphologic characteristics of the isochromosomes are not present. Persons containing the YY chromosome complement as described by Price and coworkers[7] have not manifested the breast changes which occurred in this patient.

Van Wijck and coworkers,[10] Bender and Gooch[2] and Makino and associates[5] have described karyotypes containing an elongated Y, frequently with hypospermatogenesis, but they made no mention of gynecomastia. It is unfortunate that we are unable to pursue the familial aspects of this problem. It is tempting to speculate that these phenotypic and karyotypic abnormalities are related. We believe, as do Bender and coworkers,[2] that one must be cautious about interpretations associating phenotype with chromosomal variations, especially involving the Y chromosome.

Summary

An adult male college student sought medical care because of enlarged breasts. Mastectomy was done and the pathologist's report was consistent with gynecomastia. Testicular biopsy show disorganization of spermatogenesis and hypospermia. A large Y chromosome found in the chromosome karyotype was not accompanied by other cytogenetic abnormalities in the proband. Various possibilities as to the origin of the large Y chromosome were considered.

REFERENCES

1. Barr, M. L., Carr, D. H., Soltan, H. C., Wiens, R. G., and Plunkett, E. R.: The XXYY variant of Klinefelters syndrome, Canad. Med. Assoc. J., 90:575-580, 1964.

2. Bender, M. A., and Gooch, P. C.: An unusually long human Y chromosome, Lancet, 11, 463-464, 1964.

3. Bray, P., and Josephine, S. A.: An XXYY sex-chromosome anomaly report of a mentally deficient male, JAMA, 184:179-182, 1963.

4. Cohen, M. M., Shaw, Margery, and MacCluer, Jean W.: Racial differences in the length of the human Y chromosome, Cytogenetics, 5:34-52, 1966.

5. Makino, S., Sasaki, M. S., Yamada, K., and Kajii, T.: A long Y chromosome in man, Chromosoma (Berl.), 14:154-161, 1963.

6. Patau, K.: Identification of individual chromosomes especially in man, Am. J. Hum. Genet., 12:250-276, 1960.

7. Price, W. H., Strong, J. A., Whatmore, P. B., and McClemont, W. F.: Criminal patients with XYY sex-chromosome complement, Lancet, 565-566, 1966.

8. Sandberg, A. A., Ishihara, T., Crosswhite, L. H., and Koepf, G. F.: Genotype report of a case in a male, New Eng. J. Med., 268:585-589, 1963.

9. Townes, P. L., Ziegler, N. A., and Lenhard, L. W.: A patient with 48 chromosomes (XYYY), Lancet, 1041-1043, 1965.

10. van Wijck, J. A. M., Yijdisak, G. A. J., and State, L. A. M.: Anomalies in the Y chromosome, Lancet, 218, 1962.

Obstruction of Large Bowel Due to Fecaloma

Successful Medical Treatment in Two Cases

HERVEY SEGALL, M.D., *Orange*

IT IS IMPORTANT to consider the possibility of a fecaloma in cases of large bowel obstruction. When this diagnosis is correctly made, surgical operation can be averted. The following two cases are illustrative.

CASE 1.—A 50-year-old caucasian woman entered UCLA Medical Center for the 16th time on 30 August 1965 with complaint of crampy lower quadrant pain for four days. She had not had a bowel movement in that time. The patient had had numerous abdominal surgical procedures in the past. On examination a left lower quadrant mass was palpable and high pitched sounds were heard on auscultation. The patient was mildly dehydrated but blood and urine examinations were within normal limits. Clinically, the diagnosis of large bowel obstruction was made and a plain film of the abdomen was obtained which showed a dilated transverse and descending colon with large fecal masses in the transverse colon. A barium enema was given and barium would not pass beyond a sigmoid mass despite elevation of the barium container and manual manipulation (Figure 1A). With air outlining the proximal extent of the mass, it was shown to be an elongated sausage-shaped structure (Figure 1B). On this evidence, supported by the presence of the large fecal

From the Department of Radiology, UCLA School of Medicine, Los Angeles.

Submitted 25 July 1967.

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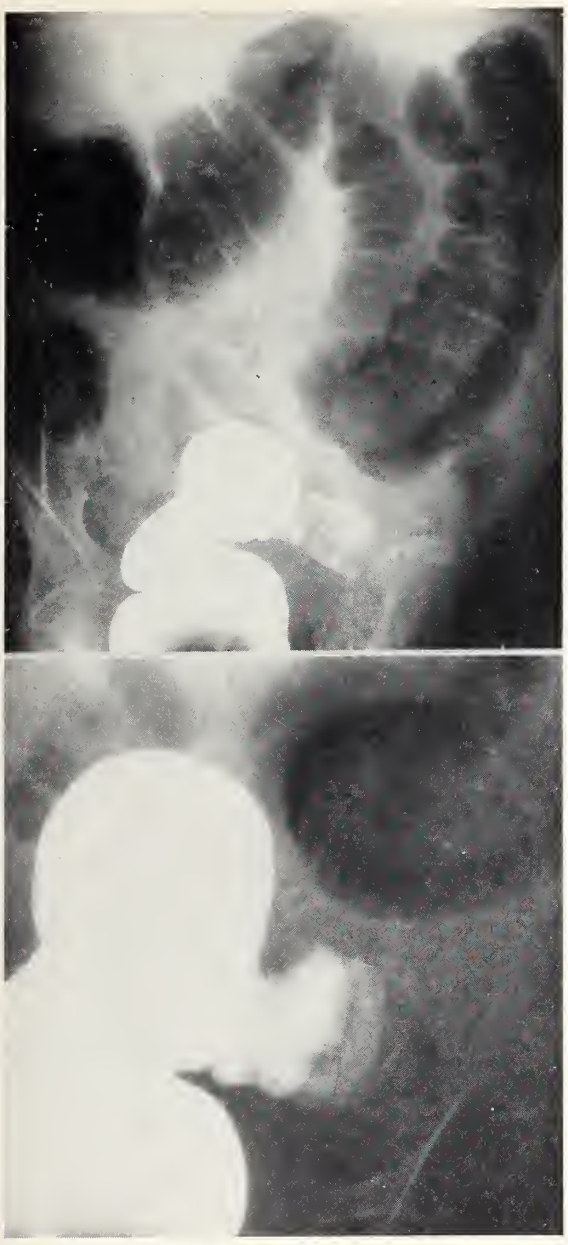


Figure 1. (Case 1)—*Above,* incomplete colon examination. Note obstruction to passage of barium in the sigmoid by the fecalith, with gas and feces distending the colon above the obstruction. The metal sutures are from a previous operation. *Lower,* "spot" film made at same examination shows outline of fecalith between barium distal to it and gas proximally in descending colon.

masses in the transverse colon, a diagnosis of fecaloma was made. Multiple lavema enemas were administered along with oral laxatives, following which the "tumor" was passed. Barium enema examination a week later showed the colon to be within normal limits.

Case 2.—The patient was a 44-year-old man with complaint of abdominal cramps, abdominal distension, nausea and anorexia of four days' duration. He had been chronically constipated and took laxatives regularly. On examination there was left lower quadrant tenderness. An x-ray film showed a rounded mass in the sigmoid region which had been coated with barium from an x-ray examination with barium by mouth one month previously. Barium enema examination was done and the mass was again demonstrated (Figure 2), although the barium was shown to pass beyond it after a temporary delay.

A day or so later, the cramps became more disabling and the patient had not had a bowel movement. He was admitted to a local hospital 29 June 1965. The abdomen was quite tender to palpation, particularly in the left lower quadrant, and active peristalsis was present. Films of the abdomen showed a dilated barium-filled colon above the sigmoid mass. A diagnosis of colon obstruction secondary to a fecal mass was made. A medical regimen, including mineral oil enemas, was instituted and opiates were discontinued. On 1 July a 6 cm ovoid firm scybala consisting of homogeneous inspissated stool was passed. A barium enema film then showed a normal descending and sigmoid colon (Figure 3).

Discussion

Reports of fecalomas producing obstruction are sparse in the American radiological literature. Childs[2] described a case in 1924 in which the fecal mass had to be manipulated and crushed before it could be expelled. The possibility of fecaloma was not considered in a case reported by Dresser[3] five years later, and the correct diagnosis was not made until the abdomen was opened. Another case in a radiology journal was reported by Feldman,[4] who considered such lesions to be rarely observed. Fecalomas may be quite large and they tend to be round and smooth. They tend to occur in the left colon, particularly in the rectosigmoid region. On occasion, layers of calcium may become encrusted upon them.[5] A diagnosis of fecaloma is supported if the mass in the colon is large, readily movable and not attached to the bowel wall.[1,6] Ordinarily, adjacent mucosal markings should be normal. A number of complications may occur, including ulceration of the bowel mucosa with resultant bleeding. Perforation may also oc-



Figure 2. (Case 2)—Spot films showing obstruction in colon at junction of descending and sigmoid. Note sharply rounded contour of inferior margin of obstructing mass, characteristic of fecalith.



Figure 3. (Case 2)—Barium enema after fecal mass was expelled, showing normal descending and sigmoid colon.

cur.[1] Obstruction is another complication, as in the cases here reported. When the diagnosis is made, laxatives and enemas may be employed. Sometimes, however, a number of days or even weeks may be required for the passage of large fecalomas in the sigmoid or descending colon.[1]

Summary

Two cases of colon obstruction secondary to fecalomas are described.

REFERENCES

1. Bockus, H. L.: Gastroenterology, Vol. 2, 835-839, W. B. Saunders Company, Philadelphia, 1949.
2. Childs, S. B.: Case report of a large fecalith, Radiology, 3:261-262, Sept. 1924.
3. Dresser, R.: A case of fecalith, Am. J. Roentgenol., 21:472-473, May 1929.
4. Feldman, M.: Fecalith of rectum: Case simulating neoplasm, Radiology, 38:89, 1942.
5. Pohl, R.: Pathology of lower colon: Fecalith of the rectosigmoid region, Roentgenpraxis, 3:337-453, Apr. 1931.
6. Schinz, Hans R., Baensch, W. E., Friedl, E., and Uehlinger, E.: English translation arranged and edited by James T. Case: Roentgen-Diagnostics, Vol. IV, pp. 3624-3625, Grune & Stratton, Inc., New York, 1954.

Interstitial Abdominal Emphysema

(Pneumatosis Cystoides Intestinalis)

RICHARD M. DAVIS, M.D., *Los Angeles*

PNEUMATOSIS CYSTOIDES intestinalis was first fully described by Bang[1] in 1876. Since that time, reports of about 385 cases have been added to the literature. The entity is now better recognized and 21 reports have appeared in the past five years.

The graphic name of the entity refers to gas-

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filled cysts which occur most commonly in the submucosa of the small and large bowel and rectum. They also occur beneath the parietal peritoneum of the liver, gallbladder, kidneys, lesser pelvis, vaginal walls, inguinal canals and mesenteries.

In most cases the lesions were associated with other pathologic conditions. If there was no other disease present, the condition was assumed to be primary.

Symptoms and Differential Diagnosis

Vomiting, or intermittent diarrhea alternating with constipation, constipation alone, melena and flatulence are the persisting complaints which usually cause the patient to seek medical attention.

In a review of 255 cases reported through 1952, Koss[6] noted that 58 per cent were associated with stenotic pyloric lesions, with vomiting the dominant symptom. Kushlan,[7] in a review published in 1962, observed that symptoms referable to intestinal obstruction were present in 85 per cent of cases. Pyloric obstruction was the cause in most cases. Alternating diarrhea and constipation and blood and mucus in the stool were noted in 15 cases reported in 1960 by Daub and Shea.[2] These cases had the one common primary symptom of pulmonary asthma of long standing.

Since the intestinal lesions most frequently seen are gas cysts located segmentally in the submucosa of the bowel, conditions that must be considered in differential diagnosis are polypoid tumors, diffuse polyposis and carcinoma of the bowel and rectum. Retroperitoneal gas, subdiaphragmatic air, pneumoperitoneum with or without mediastinal emphysema, and mesenteric cysts may be present, either alone or together.[14] One of the outstanding characteristics of pneumatosis cystoides intestinalis is that despite extensive roentgenographic, physical and perhaps sigmoidoscopic evidence of abnormality, the patient is not "toxic."

Etiology

Many etiologic theories of origin have been proposed. Bang[1] and Finney[4] attributed the condition to neoplastic change. Other investigators suggested variously that the cause was bacterial, mechanical, nutritional or due to cellular respiratory dysfunction producing intracellular gas.

In 1937, Macklin[8] reported a series of experiments in which cat lungs were cannulated and then rapidly inflated with large amounts of air. This brought about pneumothorax and pneumoperitoneum. There were also findings of interstitial air bubbles about the alveolar base, under the vascular sheath of the lung and in the mediastinum; and there were larger air bubbles along the aortic sheath to the retroperitoneal spaces and along the vascular sheaths of the aortic branches to the organs of the abdomen. Gas cysts were found subperitoneally in the liver, gallbladder, stomach and kidney as were the submucosal lesions in the small and large bowel that are typical of pneumatosis cystoides intestinalis.

In additional experiments,[9] using continual lower pressures, no evidence was found of alveolar rupture, pneumothorax or pneumoperitoneum. However, the interstitial air bubbles in the mediastinum along the aortic vascular sheath and the typical visceral emphysema were produced repeatedly.

In 1961, Keyting and coworkers[5] injected air into the root of the left lung in dogs and produced typical abdominal emphysema findings of retroperitoneal air and left colon submucosal cysts.

Elliot and Elliot[3] noted in 1963 that abdominal emphysema has been associated with numerous unrelated diseases having only the single common symptom of forced straining causing abrupt increases of the intrathoracic pressures. The distribution of the cysts from mediastinum to the submucosa of the bowel and other areas follows no regularly defined pattern other than that it is perivascular.

The origin of pneumatosis cystoides intestinalis or abdominal emphysema, as suggested by Elliot,[3] Keyting[5] and Macklin,[9] is the decompression of a silent tension pneumomediastinum secondary to chronic air leak from alveolar pores along the perivascular sheaths. Suction and pulsion of the thorax inflate the sheaths around the pulmonary arteries which are continuous with the sheaths of the aorta. Air thus gains access to the segmental aortic vascular branch distribution in the abdomen.

Diagnosis

The diagnosis is usually made by roentgenographic findings and occasionally by sigmoidoscopy[12] when the rectum and sigmoid are involved.

Roentgenographic evidence of trapped gas may be seen in any segment of the colon, rectum, small bowel, mesentery stomach or peritoneum, or of the retroperitoneal spaces.[11]

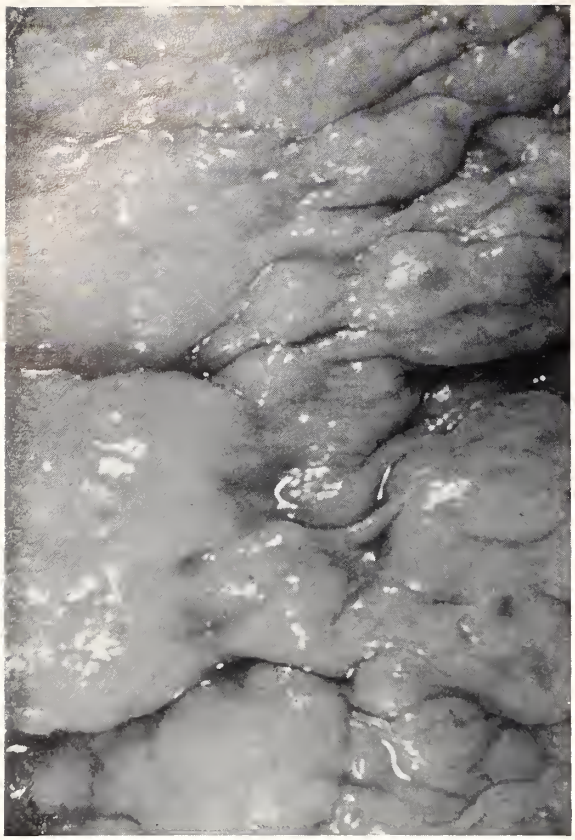


Figure 1.—Photograph of resected colon specimen demonstrating the mucosal pattern of typical "pneumatosis cystoides intestinalis" identical to that seen at sigmoidoscopy.



Figure 2.—Roentgenogram of the colon, air contrast enema, demonstrating the translucent polypoid lesions of the sigmoid and ascending colon diagnostic of the intestinal emphysema.

Underlying associated pathologic states must also be diagnosed. In cases of interstitial abdominal emphysema of the kind previously described as being "primary", enteritis with tenesmus or alternating diarrhea and constipation are present to explain the chronic intrathoracic pressure changes necessary for the abdominal emphysema to occur.

Report of a Case

Following is an additional report of a patient with abdominal emphysema.

The patient, a 57-year-old man, sought medical advice because of intermittent diarrhea with severe tenesmus and constipation for six to seven months. There was no melena, rectal bleeding or loss of weight. He had been aware of some peristaltic rushes in the abdomen, but these were not associated with pain. There was nothing in the past medical history that was pertinent to the present complaint and the results of physical examination were within normal limits.

On proctoscopic examination multiple sessile polypoid lesions were seen around the entire circumference of the rectum and sigmoid colon. The mucosa overlying these areas looked normal and no other lesions were visualized (Figure 1).

No abnormality was noted in x-ray films of the chest. X-ray examination of the colon with air contrast enema revealed multiple defects in the sigmoid and descending colon up to the splenic flexure. The remainder of the colon filled well and showed no abnormality. The characteristic findings of pneumatosis cystoides intestinalis were seen. However, the possibility of neoplasm in addition to the gas cysts could not be ruled out (Figure 2).

On surgical exploration the descending colon and sigmoid appeared to have multiple polyps although the colon was more indurated than usual. Because of the localization of the pathologic changes, segmental colon resection was done and continuity was reestablished with primary end-to-end anastomosis at the level of the rectosigmoid junction. Although the bowel was normal to palpation at this lower level, there were submucosal emphysematous lesions in the remaining rectosigmoid colon.



Figure 3.—Photograph of the saggitally cut colon specimen, showing the submucosal emphysematous cysts of interstitial abdominal emphysema.

The patient had a spontaneous bowel movement on the third postoperative day. After recovery he was examined regularly and when last seen, two years after operation, he had no unusual gastrointestinal symptoms and was in excellent health. On proctoscopic examination the rectosigmoid was observed to be normal.

Pathologist's report: The bowel had coalescent pseudopolyp-like elevations, causing the mucosa to be thickened. They proved to be small air-filled loculi divided by tissue-paper thin, glistening fibrous septa (Figure 3). These lesions were so coalescent that in most areas, even a probe could not be inserted between them. The mucosa was intact (Figure 4). The microscopic findings were consistent with the interstitial location of these cysts and inconsistent with theories of intralymphatic location.

Discussion

The differential diagnosis of abdominal emphysema, or so called pneumatoses cystoides intestinalis, is sometimes difficult if only a small segment of bowel is involved. Bizarre findings associated with this condition elsewhere in the abdomen can be quite misleading. The air follows a route, sometimes quite obscure, from the mediastinum to a location in the abdominal cavity. The condition can be associated with relatively minor disease, such as a nonspecific enteritis.

A dominant characteristic is that the patient is not as sick as he might be expected to be from the x-ray or sigmoidoscopic findings.

Conservative therapy is certainly desirable. The disease underlying the chronic obstruction should be treated, and often when this is done the abdominal emphysema will disappear.

If diagnosis cannot be made accurately by other means, laparotomy should be done. In a few cases



Figure 4.—Photograph of the resected colon specimen, showing the typical segmental distribution of the polypoid colon lesions of interstitial abdominal emphysema.

involving the colon, the obstructive symptoms present may be due to the development of abdominal emphysema; and colon resection then may be necessary to change the cycle of events, as in the case here reported.

The abdominal emphysematous condition probably exists in far more patients than are being reported.[13] It is not a disease listed in the Standard Nomenclature index, but is a condition secondary to an unusual physiological and anatomical circumstance in which routes are opened to the passage of air from the lungs to the abdominal cavity and to organs along the aortic vascular branches.

The condition is produced by a chronic, abrupt increase in the intra-alveolar air pressures sufficient to cause air to travel through the alveolar pores and become trapped under vascular sheaths. The severity and chronicity of pulmonary strain (as in coughing) and the physiological variance of alveolar pore function (loss of elasticity, for example) determine the extent of the abdominal emphysema.

It seems to the author that the term *pneumatosis cystoides intestinalis* might best be discarded for the more adequate *interstitial abdominal emphysema,* since all organs and spaces of the abdominal cavities are affected.

This is a reversible condition, as well as a recurrent one. There have been no cases of death recorded as a result of abdominal emphysema.

Summary

The condition called pneumatosis cystoides intestinalis is not a disease but is abdominal emphysema produced by "silent" air leakage from the alveolar pores of the lung along perivascular routes to the mediastium, aortic vascular sheaths, to the abdominal distribution of the aortic branches, and to the retroperitoneal spaces. A better term for it is interstitial abdominal emphysema. A common precursor is chronic, abrupt increases of intra-alveolar air pressure secondary to straining, coughing or vomiting. Treatment depends upon the nature of the concurrent disease causing the obstructive symptoms.

In the case here reported, operation was carried out because, although diagnosis was made on proctoscopic and radiographic evidence, the possibility of neoplasm could not be ruled out. A segment of the sigmoid colon containing multiple gas cysts was resected. The patient recovered and had no further difficulty.

REFERENCES

1. Bang, B. L. F.: Nord. Med. Ark., (No. 18), 8:1, 1876.

2. Boub, H. P., and Shea, J. J.: Pneumatosis cystoides intestinalis. JAMA, 172:1238-42, Mar. 1960.

3. Elliot, G. B., and Elliot, K. A.: The roentgenologic pathology of so-called pneumatosis cystoides intestinalis, Amer. J. Roenten., 89:720-9, Apr. 1963.

4. Finney, J. M. T.: Gas cysts of the intestine, JAMA, 51:1291, 1908.

5. Keyting, W. S., McCarver, R. R., Kovaril, J. L., and Daywitt, A. L.: Pneumatosis intestinalis: a new concept, Radiology, 76:733-41, May 1961.

6. Koss, L. G.: Abdominal gas cysts, Arch. Path., 53: 523-49, June 1952.

7. Kushlan, S. D.: Pneumatosis cystoides intestinalis. Report of a case mimicking irritable bowel syndrome with x-ray diagnosis and resolution, JAMA 179:699-702, 3 March 1958.

8. Macklin, C. C.: Pneumothorax with massive collapse from experimental local over-inflation of lung substance, Canad. Med. Ass. J., 36:414-420, Apr. 1937.

9. Macklin, C. C.: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: clinical implications, Arch. Intern. Med., 64:913-26, Nov. 1939.

10. McGregor, J. K., and McKinnon, D. A. J.: Intestinal interstitial emphysema, Gastroenterology, 35:206-11, Aug. 1958.

11. Ritvo, M., and Shauffer, I. A.: Gastrointestinal x-ray diagnosis, Lea & Febiger, Philadelphia, 1952.

12. Smith, W. G., Anderson, M. J., Jr., and Pemberton, H. W.: Pneumatosis cystoides intestinalis involving the left portions of colon: report of four cases diagnosed at sigmoidoscopy, Gastroenterology, 35:528-33, Nov. 1958.

13. Swerdlow, Hyman: Pneumatosis cystoides intestinalis: characteristics and report of four cases, Dis. Colon & Rectum, 7:306-8, July-Aug. 1964.

14. Williams, M. J., Sutherland, D. H., and Clark, C. G.: Lymphosarcoma of the small intestine with a malabsorption syndrome and pneumatosis intestinalis: report of a case with peroral jejunal biopsy, Gastroenterology, 45:550-7, Oct. 1963.



Hyperglobulinemic Purpura

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. STRAND*: A 22-year-old Portuguese woman was admitted to hospital because of red spots on her legs. Her present illness began in 1962 when she first noticed the appearance of dark red spots on her feet and ankles, which disappeared spontaneously in three to four days. Over the ensuing three years she had recurrent episodes of petechiae over her ankles and feet. In 1963 she was found to have a serum globulin level of 2.3 gm per 100 ml, and a diagnosis of hyperglobulinemic purpura was made. Because of exacerbation of the purpura with spreading to the arms and thighs, she was admitted to hospital at this time. She had had no previous history of epistaxis, hematuria or rectal bleeding, but following her first pregnancy severe postpartum hemorrhage developed. Her next pregnancy was uncomplicated.

Examination of the skin showed resolving petechiae and purpuric lesions over the feet, ankles, thighs and arms. There were many hyperpigmented macules over the dorsum of the feet and ankles. No significant lymphadenopathy was present. The liver and spleen were both palpable two fingerbreadths below the right and left costal margins respectively. Funduscopic examination was within normal limits.

Laboratory data: Hemoglobin 11.8 and 12.8 gms per 100 ml; packed cell volume 37 per cent; a smear of peripheral blood showed rouleaux formation of the red blood cells: leukocyte count 3,000 and 4,000 per cu mm with 36 per cent lymphocytes on differential count. Platelet count was within normal limits and reticulocyte count was 1 per cent. No abnormality was noted on examination of bone marrow aspirate. Clotting time, bleeding time and prothrombin time were within normal limits. Results of a test for antinuclear factor and of several lupus erythematosus tests were negative. Latex fixation was positive at a titer of 1:260; leukocyte alkaline phosphatase level was 32 units (normal 20-70 units). Tests for serum cryoglobulins were negative and serum complement levels were within normal limits. Total protein levels varied between 7.0 and 9.5 gm per 100 ml with a relative and absolute increase in the gamma globulin component (Figure 1). Creatinine clearance was 94 ml per minute. Results of pulmonary function tests were within normal limits. The patient's renal acidification mechanism, tested with an ammonium chloride infusion test,† was judged to be borderline normal.

DR. SMITH*[2]: I do not believe there are any x-ray films to demonstrate on this patient, but she herself is here for presentation. (Patient enters.)

DR. SMITH: How are you feeling?

PATIENT: Fine, thank you.

DR. SMITH: What is the major problem that has been bothering you recently?

PATIENT: The recurrence of the spots on my leg.

*James Strand, M.D., Intern in Medicine.

†Performed by Dr. R. Curtis Morris.

*[2]Lloyd H. Smith, Jr., M.D., Prof. & Chmn., Dept. of Medicine.

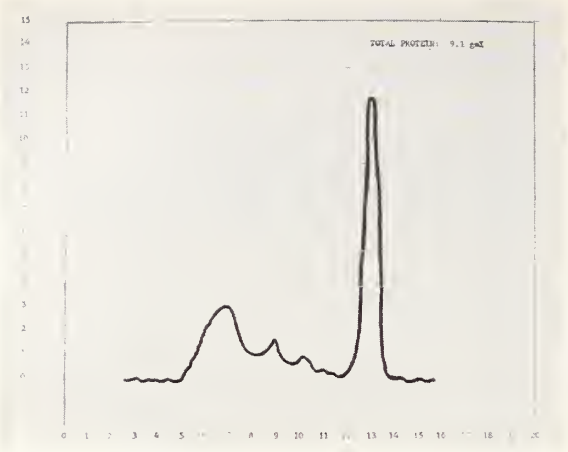


Figure 1.—Cellulose acetate electrophoretic pattern of the patient's serum, demonstrating a broad based gammaglobulin elevation. The total protein is 9.1 grams per 100 ml. (The vertical column of figures indicates the relative optical density. The horizontal measures electrophoretic mobility. The anode is to the left.)

DR. SMITH: Are they uncomfortable?

PATIENT: They are painful at times. My legs may become swollen and I can hardly walk.

DR. SMITH: Can you predict when these spots will appear on your legs?

PATIENT: No, but I usually notice them when I become tired.

DR. SMITH: Are they related to activity—to standing, or walking or dancing?

PATIENT: Yes, to all of these things.

DR. SMITH: Dr. Salmon, is there anything you would like to bring out?

DR. SALMON*[3]: Does taking alcohol give you some trouble also?

PATIENT: Yes, it brings out the spots.

DR. SALMON: Do you notice any relationship to the weather?

PATIENT: No—except in the winter I feel much better, and in the summer I feel worse. Warm rooms bother me the same way. (Patient leaves.)

DR. SMITH: This is an extremely interesting syndrome which has been referred to as hyperglobulinemic purpura. We have asked Dr. Salmon to review this entity. What is the link between the elevation of serum globulins and purpura, Dr. Salmon?

*[3]Sydney E. Salmon, M.D., Research Fellow in Medicine.

DR. SALMON: Your question regarding the link between the elevation of globulin and the purpura is of extreme interest, Dr. Smith. That question was first raised when the syndrome was described by Jan Waldenstrom in 1943[8] while discussing methods of protein isolation. At that time he postulated that there was a relationship between elevation of the gamma globulin and the appearance of the purpura. A mechanism to explain this relationship has yet to be clearly formulated, although as I will discuss subsequently, at least one of the protein abnormalities in this syndrome may represent a significant factor in the pathogenesis of the purpura. In certain respects the syndrome of hyperglobulinemic purpura is a medical curiosity, but for the patient we have seen today it is a considerable problem. It is partially a cosmetic problem, but she does have pain at the sites of the lesions and it concerns her a great deal. From the standpoint of the consulting hematologist, immunologist or internist who sees a patient such as this, it is of interest because the patient is often referred for evaluation of far more dire illness such as lymphoma or multiple myeloma.

This purpuric syndrome seems to be considerably more benign than the neoplastic dysproteinemias. I have had opportunity to study several patients with this disorder. One of them is also a woman in her 20's, also of European origin; she too, has similar difficulties with alcohol, dancing and warm weather. Because of the related stresses inducing the purpuric attacks, I thought the name, Saturday Night Purpura, might be appropriate. Dr. Fudenberg, in the way he likes to make neologisms, thought it should be called the WASP syndrome, and in one fell swoop include the Watusi, alcohol, Saturday night and purpura too. However, the Watusi is likely to become passé and the patient is likely to continue to have her problems when some new dance is in vogue, leaving us with an outmoded name. The etiologic lineaments of this disorder are obscure, but in the 40 or so cases that have been reported in the world literature, most of the patients have come from Europe; and in most of the cases that have been reported from the United States, if the origin of the patient was stated, it was noted that they had begun life in Europe and had moved to the United States somewhat later. This may be only a straw in the wind, but here may be some possibility that there may be a genetic predisposition or some environmental factor present in their homelands,

although they have been reported from Sweden, Germany, France and Spain—in fact from most of the countries in Europe. What environmental factor could be distributed this widely is hard to imagine. Many of the patients give a history of an adolescent rheumatic fever-like illness or pleurisy, so conceivably some initial microbial antigenic insult may induce a state of chronic stimulation of the immune system.

There are several pertinent observations in this syndrome from the hematologic standpoint. The peripheral blood often shows mild to moderate leukopenia and rather pronounced rouleaux formation, while the platelet count and red cell indices are normal. These findings exclude the purpura seen in patients with a number of kinds of more dire illnesses, such as acute leukemia and systemic lupus erythematosus, as well as other disorders associated with thrombocytopenia. The bone marrow in these patients is usually normal, although there is occasionally a slight increase in plasma cells and I think that was the case with this patient. There is also often lymphadenopathy or hepatosplenomegaly. Skin biopsy in cases of this kind show a perivascular infiltration of the skin with lymphocytes and some degree of endothelial proliferation.[1]

I would like to review some of the observations we had an opportunity to make in the case of today's patient and on one other patient I mentioned who seems to have the same symptoms. Lymph node biopsy (Figure 2) showed decided lymphoid hyperplasia with increased size of the sinusoids and an increase in mature plasma cells, but without extension of lymphoid elements beyond the capsule.

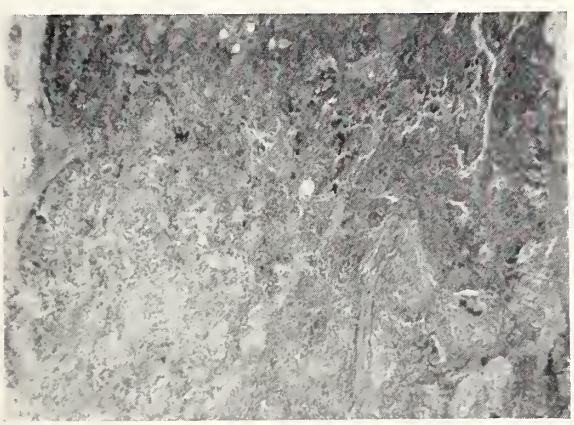


Figure 2.—Hematoxylin and eosin stained section of a lymph node in hyperglobulinemic purpura. The node is hyperplastic and there are numerous plasma cells along the sinusoids. (×100)

Serum protein electrophoresis in today's case showed a pronounced increase in the beta to gamma globulin region. This is obviously a diffuse elevation of gamma globulin, as this peak encompasses the migration area of the major immunoglobulins and includes molecular species of differing electrical mobility. Electrophoresis alone is not sufficient to characterize the immune abnormality.

To further clarify the nature of the protein abnormalities, immunoelectrophoresis is quite helpful. This procedure is somewhat similar to ordinary paper electrophoresis, except that after the electrophoretic run, troughs are cut parallel to the protein migration and specific antisera are added so that a series of arcs is developed as the result of antigen-antibody interaction. Immunoelectrophoretic studies on the patient we are discussing today demonstrated a diffuse increase in the gamma G globulin as well as the presence of both kappa and lambda light chain determinants of gamma G globulin molecules. These immunoelectrophoretic findings differ decidedly from the findings in typical multiple myeloma or macroglobulinemia, in which a focal increase in the affected immunoglobulin usually occurs (M-component) and gives the appearance of a narrow discrete bowing of the precipitation arc. In addition, the purified protein from a patient with malignant dysproteinemia, characteristically has only a single light chain type, kappa or lambda, but not both. In plasma cell myeloma or macroglobulinemia, presumably only a single clone of neoplastic cells proliferates and produces the diagnostic protein abnormality, whereas in an illness such as that manifested in the patient we have just observed, it would appear that many different clones of immunocompetent cells proliferate and synthesize diverse immunoglobulin molecules.

Specific immunoquantitative levels have confirmed an isolated increase in gamma G globulin. In both of the patients I am discussing, there was a pronounced increase in gamma G globulin whereas the gamma A and gamma M globulins were in the normal range. Serial serum samples over the past year have shown some variation in absolute quantities, although the relative proportions of the three globulins remained fairly constant. In the family history of today's patient there

is no evidence of a familial immune defect among first order relatives.

I have been interested in the lymphocyte culture of peripheral blood from both of these patients. If normal peripheral lymphocytes are isolated and allowed to incubate in a tissue culture system for about 72 hours, usually one sees very little change in the total cell number or in the morphologic features of the cultured cells. In contrast, if one adds a mitogenic agent such as phytohemagglutinin (PHA) or an antigen to which the patient has been previously immunized, pronounced cellular changes occur. Morphologically there is a rounding up and increase in cell size, and the cells undergo mitotic division, so that the total number of cells in culture increases and the cells take on a more primitive blast-like appearance. The biochemical concomitants of these changes include a decided increase in the synthesis of cellular deoxyribonucleic and ribonucleic acid (DNA and RNA) and protein as measured by the incorporation of radioactively labelled precursors into the macromolecules. In certain disease states, most notably Hodgkin's disease, and acquired agammaglobulinemia,[7] there is a notable impairment of the ability of cells to undergo this series of biochemical transformations, and they remain more like resting cultures.

In similar studies on both patients with hyperglobulinemic purpura, the control cultures showed no stimulation, and the PHA-stimulated cultures underwent normal DNA, RNA and protein synthesis.[5] The cells were in no way over-reactive in vitro. These findings imply something that perhaps is clarified by examining the patient. The enlarged lymph nodes, liver and spleen undoubtedly reflect the increased number of cells producing immune globulins without implying that the individual lymphoid cells are over-reactive.

There are some other immunological findings that are of definite pertinence. When one tests the serum of these patients for the presence of anti-gamma globulin activity ("rheumatoid factor"), positive tests of moderate titer by either latex fixation or more sensitive methods are commonly noted. This is an abnormality seen characteristically in these patients.

Analytical ultracentrifugation of the serum of these patients has not only confirmed an increase in 7S gamma globulin but also has demonstrated the presence of a considerable amount of an "intermediate site complex" in the range of 9-16S. These findings have been also observed in several previously reported cases. The complex may represent a form of immune globulin polymer or soluble antigen-antibody complex, such as an anti-gamma globulin antibody in combination with gamma G globulin. The rheumatoid factor of rheumatoid arthritis has been demonstrated to be antibody-antigen complexes of considerably higher S value (at least 21S) because the antibody in the complex is usually a macroglobulin antibody.[2] The composition of the complex in hyperglobulinemic purpura, which has yet to be fully characterized, could be related to the pathogenesis of the purpura. Evidence has recently been offered[6] that complexes of DNA and anti-DNA antibodies, which occur in patients with systemic lupus erythematosus, are deposited in the renal glomerulus at the time of clinical symptoms and play a role in the pathogenesis of lupus nephritis. Conversely a similar mechanism may be involved in the production of the cutaneous lesions in hyperglobulinemic purpura. If the hypothesis of complex-induced vascular damage has reference in this syndrome, the physiochemical and immunologic properties of the complex must be considerably different than of the complexes seen in lupus patients, inasmuch as evidence of gross renal damage is not seen in hyperglobulinemic purpura. Fluorescent antibody tracing studies of the skin lesions have not demonstrated deposition of immune globulin,[1] in contrast to the situation observed in the kidney in lupus nephritis. Other evidence of immunologic abnormalities from the standpoint of collagen disease or vasculitis is absent: namely, tests for antinuclear antibodies and lupus preparations are negative. An additional and significant laboratory finding is that carefully done cryoglobulin studies were negative. A syndrome involving mixed cryoglobulins and renal disease has been reported by Meltzer and Franklin[3], but it appears distinctly different from hyperglobulinemic purpura.

Many patients with hyperglobulinemia seem to have a defect in renal tubular acidification.[4] When blood from today's patient was tested by ammonium chloride loading, the result was at the lower end of the normal range, so that we cannot say too much in that regard about her.

With regard to the relationship of this disease to other disease states, it can be stated that, by and large, this seems to be a benign disease.[9] It usually does not require any specific form of therapy beyond reassurance. Some patients have been

treated with corticosteroids usually without benefit or even on occasion with alkylating agents or other cytotoxic agents.

There have been a few scattered reports of patients such as this in whom lymphoma, myeloma, or systemic lupus has subsequently developed. These reports are extremely few in number, and the protein abnormality has not always been well documented immunologically.

Most of the things I have said about hyperglobulinemic purpura can be summarized simply. The clinical findings in this syndrome include purpura after exercise, exposure to heat or alcohol, and occasionally after coming in out of the cold. Lymphadenopathy and hepatosplenomegaly are frequently present, and the clinical course is usually benign. Lymphoid hyperplasia is found in peripheral lymphoid tissues, and also perivascular infiltrates in the skin. One thing which we did not demonstrate in today's patient, although it is present, is cutaneous hemosiderin deposition, especially around the ankles. After a patient has had this illness for five years or so, there is considerable blackish discoloration around both ankles in addition to the sites where various purpuric lesions have appeared. Abnormal results of laboratory studies include an increase in the blood sedimentation rate, diffuse hypergamma G globulinemia, the presence of intermediate complexes on ultracentrifugation, and positive rheumatoid factor tests (which may reflect antigammaglobulin antibodies of a kind different from those of rheumatoid arthritis). Lymphocyte transformation studies in these patients show no abnormality, and other pertinent negatives include studies of cryoglobulin, antinuclear factor and LE preparations.

DR. SMITH: Thank you, Dr. Salmon. I think that is an excellent summary of a complex subject. Has plasmaphoresis been tried, to see if this would prevent the appearance of lesions under the stress of Saturday night activities?

DR. SALMON: This was not mentioned in the clinical course. We did have the opportunity for extensive plasmaphoresis in today's patient when she was in the hospital, and over the course of four days eight units of plasma were removed. One day after plasmaphoresis was completed, the patient took a week-end pass and went out Saturday night. Monday morning she returned to the hospital, complete with purpura. Clearly there was no immediate change seen with plasmaphoresis, and a more Herculean effort at doing this was not attempted at the time. One common denominator before the appearance of purpura seems to be vasodilatation, due usually to alcohol, warmth and exercise. I made a few therapeutic trials with cutaneous vasoconstrictors, such as pseudoephedrine hydrochloride (Sudafed®), and these had no effect whatsoever.

DR. SMITH: Dr. Kunkel, would you like to make some remarks about the problem presented by this patient?

DR. KUNKEL*[4]: Recently we had under observation a nurse with symptoms similar to those presented by this patient. Every Sunday morning she has purpura of the ankles. She is an expert dancer, and this problem usually occurs only after Saturday night dancing. In her case there is pronounced elevation of gamma globulin levels and a large number of the intermediate complexes that Dr. Salmon has discussed. We have been intrigued by the possibility that large size gamma globulin complexes are directly involved in the purpura in these cases. One of the aspects that has interested us is the fact that, although having these gamma globulin complexes, these patients do not have renal disease. Perhaps these complexes are small enough to be relatively benign. Apparently they do not fix complement, because in our cases complement levels have been normal.

The other question that has interested us is that the condition is seen predominantly in female patients, a situation reminiscent of lupus erythematosus. One wonders whether these cases do not fall into the general category of the connective tissue diseases. They do not have the manifestations of systemic lupus erythematosus, in that antibodies are not present. Dr. Waldenstrom told me that in some of his original cases Sjogren's syndrome developed subsequently—which leads to this question: Were any eye signs present in this patient?

DR. STRAND: There have been no such signs as yet.

DR. SMITH: I was surprised to learn that the prognosis is so benign, and in addition that this syndrome had been so clearly defined as an entity. It was my memory that some patients showed progression to Sjogren's syndrome, but I thought that more patients had later come to have lupus erythematosus. The majority of patients, followed for 20 years now, have had a benign course.

*[4]Henry G. Kunkel, M.D., Professor of Medicine, Rockefeller University, New York.

PHYSICIAN IN AUDIENCE: At what age is this entity recognized? Is it recognized in early childhood or during puberty?

DR. SALMON: In the reported cases the age range has been from young adulthood to women in their 40's. Relative to these patients there is some confusion about the case reports of allergic purpura or Henoch-Schonlein's purpura in children. In the former the gamma globulin levels are normal. The total number of cases of hyperglobulinemic purpura is still somewhat small, and a definitive answer cannot be given.

PHYSICIAN IN AUDIENCE: I wonder if Dr. Salmon would say a few words about the genetics of the disorder. I understand there are a few instances in which family members have actually had decreased amounts of immune globulins.

DR. SALMON: This is correct. One family that Waldenstrom studied had a variety of related disorders including several members with systemic lupus or discoid lupus, one with hyperglobulinemia and another with hypergammaglobulinemic purpura. This is perhaps the exception rather than the rule, although certain other familial instances of connective tissue disorders have been seen. When I spoke of this earlier in my discussion I was alluding only to studies we did on the family of today's patient. We had several generations to study and there was no evidence of familial incidence of connective tissue or immunologic disorder.

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REFERENCES

1. Carr, R. D., and Heisel, E. B.: Purpura hyperglobulinemia, Arch. Dermat., 94:536, 1966.

2. Kunkel, H. G., Muller-Eberhard, H. J., Fudenberg, H. H., and Tomasi, T. B.: Gamma globulin complexes in rheumatoid arthritis and certain other conditions, J. Clin. Invest., 40:117, 1961.

3. Meltzer, M., and Franklin, E. C.: Mixed cryoglobulinemia, Am. J. Med., 40:828, 1967.

4. Morris, R. C., Jr., and Fudenberg, H. H.: Impaired renal acidification in patients with hypergammaglobulinemia, Med., 46:57, 1967.

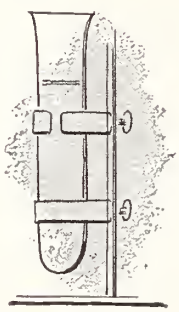
5. Salmon, S. E., and Fudenberg, H. H.: Metabolic and immunologic studies in hyperglobulinemic purpura. In preparation.

6. Tan, E. M., Schor, P. H., Carr, R. I., and Kunkel, H. G.: Deoxyribonucleic acid (DNA) and antibodies to DNA in the serum of patients with systemic lupus erythematosus, J. Clin. Invest., 45:1732-1740, 1966.

7. Tormey, D. C., Kamin, R., and Fudenberg, H. H.: Quantitative studies of phytohemagglutinin induced DNA and RNA synthesis in normal and agammaglobulinemic leucocytes, J. Exp. Med., 125:863-872, 1967.

8. Waldenstrom, J.: Clinical methods for the determination of hyperproteinemia and their practical value for diagnosis, Nord. Med., 20:2288, 1943.

9. Waldenstrom, J.: Three new cases of purpura hyperglobulinemia: A study in long-lasting benign increase in serum globulin, Acta Med. Scand., Suppl. 226, 931, 1952.



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California Medicine

EDITORIAL

A Great Editor

THE NEW editors of CALIFORNIA MEDICINE have a distinct feeling of having suddenly stepped into the very large shoes and been called upon to don the mantle of a man whose breadth of shoulder and very considerable stature have become apparent to all the readers of this journal. Dwight L. Wilbur served conscientiously and ably as Editor for twenty-one and a half years. During that time the journal has moved from one which largely reflected, in visual form, what went on at the annual sessions of the California Medical Association to one which has developed many and varied sources of manuscripts. Under Dr. Wilbur's steady hand it has consistently grown, not only in size and circulation but in the sophistication and quality of content. It has taken its place among the foremost and most widely read of state medical journals.

Dr. Wilbur did not leave CALIFORNIA MEDICINE without expressing his vision of its future. He observed that the number of excellent medical schools in California and in the West is growing. He noted that the California Medical Association has become a leader in the socio-economics of medicine and in developing new relationships with government. He believes that CALIFORNIA MEDICINE should reflect these activities of the present and future and that it should grow in prestige and value as it does so. He envisions first a regional and then a national medical journal of increasing stature which will reflect great credit upon the California Medical Association and the medical profession of California.

CALIFORNIA MEDICINE, along with the California Medical Association, is proud to contribute its great editor to even greater greater service to his profession and his fellow man at the national level. His successors, between them, will try somehow to fill his very large shoes and then, if the metaphor be not too incredible, climb upon his very broad shoulders and add something further to the stature of his *arbeit* of two decades and more.

Choriocarcinoma, a Landmark In Cancer Chemotherapy

THE DEVELOPMENT of effective means of therapy for disseminated cancer has proved to be one of the most complex and difficult tasks in all of medicine. The article by Johnson, Jacobs and Silliphant in this issue of CALIFORNIA MEDICINE, on the treatment of choriocarcinoma and related trophoblastic neoplasms of the uterus, underscores and extends our knowledge of the most successful application thus far of cancer chemotherapy in man. Choriocarcinoma has remained for over a decade[2] as the only disseminated neoplasm in adults where intensive chemotherapy can induce

remissions in most patients as well as cures in a sizable proportion of those treated. The dramatic clinical responses are the result of collaborative efforts by tumor biologists, endocrinologists and clinical investigators interested in deciphering the puzzle of trophoblastic tumors.

The observations of occasional spontaneous complete remissions of choriocarcinoma as well as the relative sensitivity of this neoplasm to a whole host of chemotherapeutic agents of differing classes — antimetabolites, antibiotics, alkylating agents and plant alkaloids — distinguish it from all other human neoplasms. In view of the origin of choriocarcinoma from the placenta, which is derived from both parents, it is possible that certain factors of host resistance directed against transplantation antigens may also play a role in the oncolysis associated with chemotherapy.

Precise quantitation of those products of tumor cell metabolism which can serve as biologic indicators of occult neoplastic mass has proved to be of considerable importance to clinicians. The synthesis of gonadotropins is normally restricted to the pituitary and the placenta. Human tumors which have trophoblastic elements — choriocarcinomas, teratomas, and embryonal-cell carcinomas — are the most frequent neoplasms which can produce gonadotropins, although gonadotropic activity has also been found in four instances of bronchogenic carcinoma[1] and several of hepatoma.[4] Quantitation of human chorionic gonadotropin (HCG), initially by bioassay and recently by more sensitive immunoassay, has not only aided in diagnosis and staging of trophoblastic tumors but has provided guidelines for clinicians as to the relative efficacy of chemotherapy, and to the duration of therapy required to attain a probable cure in patients with responsive neoplasms.

Other disseminated neoplasms regularly elaborate metabolic products which can be precisely measured; for example, the paraproteins of multiple myeloma, steroid hormones by adrenal, ovarian and testicular neoplasms, acid phosphatase by prostatic carcinoma, and lysozyme in monocytic leukemia.[3] In these tumors, drug-induced remissions can also be monitored by falling levels of the secretory product; however, the product usually remains detectable albeit at reduced levels, and cures have yet to be observed with present forms of therapy. It can be anticipated that the list of human neoplasms which are found to regularly elaborate products that can be quantified, will grow progressively. As additional forms of therapy become available to oncologists, studies of tumor products will undoubtedly play a central role more frequently in diagnosis, staging and "therapeutic titration." The concept of prolonged total suppression of tumor product secretion by chemotherapy — a concept which appears to be justified in choriocarcinoma — may well prove applicable in other forms of disseminated cancer.

REFERENCES

1. Fusco, F. D., and Rosen, S. W.: Gonadotropin-producing anaplastic large-cell carcinomas of the lung, New Eng. J. Med., 275:507-515, 1966.

2. Li, M. C., Hertz, R., and Spencer, D. B.: Effect of methotrexate therapy on choriocarcinoma and chorioadenoma, Proc. Soc. Exper. Biol. Med., 93:361-366, 1956.

3. Osserman, E. F., and Lawlor, D. P.: Serum and urinary lysozyme (muramidase) in monocytic and monomyelocytic leukemia, J. Exp. Med., 124:921-928, 1966.

4. Reeves, R. L., Tesluk, H., and Harrison, C. E.: Precocious puberty associated with hepatoma, J. Clin. Endocr., 19:1651-1660, 1959.

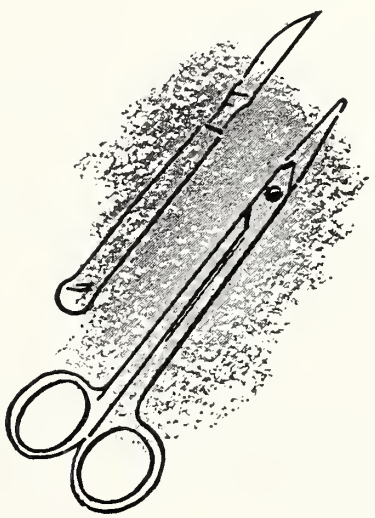
A Third Force

RECENT EVENTS in the Medi-Cal program have focused attention on two separate value systems in health care. One system, which might be called humanitarian, is grounded in the premise that everyone is entitled to all the health care he needs and that the best of what modern medicine has to offer should be readily available to him when he needs it. The other, which might be called economic, recognizes that there will probably always be insufficient health care resources to meet this demand, and seeks to identify and make the most efficient use of what can be made available. Each of these value systems appears to have strong support from the public and there seems to be a general public expectation that somehow the aims of both will be accomplished.

Recent events suggest that if either of these value systems is neglected, public opinion will rally to its support. Indeed, proposals of severe restrictions in the Medi-Cal program evoked a hue and cry in support of humanitarian values; and at almost the same time widely publicized allegations of over-use and overcharging led to clear warnings

of strong public support for economic values, even though the allegations were almost immediately proved false.

California physicians find themselves generally in sympathy with the public desire that somehow the aims of both value systems be achieved in health care whether the auspices be public, private or some combination. The California Medical Association leadership has been gradually developing an appropriate role for organized medicine. The recent Council "Statement of Principle on Medi-Cal" (adopted by the Council 4 November 1967) decisively placed organized medicine in California in the role of a sympathetic and powerful advocate for the public's desire to realize the advantages of both the humanitarian and the economic value systems in health care. Implicit in this attitude is a recognition that each value system will have its own advocates who will advance their cause with whatever expertise and pressure they can bring to bear, and that therefore a third force of advocacy will be needed to achieve and maintain a reasonable balance between the two. It is also implicit in the Council's statement that the expertise and experience of the medical profession can and should become this third force. The CMA leadership is to be commended for taking this important step.



A Commendation from the Council

Whereas, Dwight L. Wilbur, M.D., as a member of the California Medical Association for the past 29 years, has given tirelessly of his time and wisdom; and

Whereas, his achievements in all phases of medicine at the local, state and national level are without equal; and

Whereas, he has served with dedication and distinction as the editor of the journal of the California Medical Association continuously for the past twenty-one and a half years; and

Whereas, he has provided inspirational and responsible leadership as a member of the Council of the California Medical Association since 1946; and

Whereas, he has given freely of his abilities as a member of the California Delegation to the AMA for twelve years, holding the chairmanship of the Delegation for two years; as a member of the AMA Board of Trustees and currently as President-Elect of AMA; and

Whereas, honors bestowed upon him include the presidencies of the American College of Physicians, the American Gastroenterological Association, the California Academy of Medicine, and the Alumni Association of Mayo Graduate School of Medicine; and

Whereas, he has made countless other major contributions to the betterment of medicine throughout his career of distinguished service; and

Whereas, Doctor Wilbur has earned the respect and admiration of his colleagues everywhere; therefore, be it

RESOLVED: That the California Medical Association expresses its deepest appreciation and gratitude to Dwight L. Wilbur, M.D., for his peerless leadership and unparalleled contributions to all of medicine and to the California Medical Association.

California Medical Association

NOTICES AND REPORTS

A Parting Word to the Council

The following remarks were addressed to the Council of the California Medical Association at its 4 November meeting by Dwight L. Wilbur as a valedictory in anticipation of his retirement from the editorship of CALIFORNIA MEDICINE *and his seat on the Council:*

I WOULD LIKE to say a word or two about the experience I have had on the Council of the California Medical Association, because I think that I have sat on this Council longer than anyone else — certainly in modern times — and there is no one in the room here, with the exception of "Hap" Hassard, who has sat with it longer. Hap, of course, knows more about its history than I do; but having served under six chairmen of this Council, I must say that I have had a very remarkable experience. It has been a great privilege for me, and I think that much of what I have learned about legislation and socio-economic matters, I learned here on this Council. I can say without any question that in my judgment the Council of the CMA is the most effective deliberative body in organized medicine in this country. And I think the best evidence of that is not my opinion, but how the CMA stands in this state and particularly how it stands nationally.

Now I am old enough so that I am going to take the liberty, because I can't resist, of giving you just a little advice—three points:

1. The first is that I hope you will maintain unity of purpose—not unity, but unity of purpose. At times there has been, of course, as there always is in a body of this sort, a certain degree of faction. This is understandable, and it is good as long as it doesn't last too long and as long as it doesn't go too deep; but if the Council will maintain unity of purpose, then one has no fear about the future of the CMA.

2. The second bit of advice I would like to give you is to be sure to maintain the private practice of medicine no matter what else you do, because the free enterprise system and the market place are the bases of American democracy and success and they are biologically sound. And because they are biologically sound, they are right. And along with that I think it is very important to think of the physician-patient relationship as the essence of this and to recognize that the heart of the art of medicine can be expressed by the voluntary association of two people, one giving and the other seeking relief.

3. Now the third item of advice which I offer to the Council is to continue to think of the patient as a person—as a person in whatever he is doing as an individual, and as a person in respect to his family and his community. I think one of the reasons for the California Medical Association's present position of leadership is that it *has* considered the patient as a person apart from his visit to a physician's office and in relation to his job, his family and his community—in other words, the relationship of medicine to society.

If the Council will follow these three bits of advice I have no question about the future of the effectiveness of the Council of the California Medical Association.

In Memoriam

Balfour, Donald Church, Jr., San Marino. Died 26 November 1967 in San Marino, aged 51. Graduate of Northwestern University Medical School, Chicago, Illinois, 1943. Licensed in California in 1950. Doctor Balfour was a member of the Los Angeles County Medical Association.

⁂

Blumstein, Samuel, Los Angeles. Died 8 November 1967 in Los Angeles, aged 50. Graduate of Philadelphia College of Osteopathy, Philadelphia, Pennsylvania, 1940. Licensed in California in 1946. M.D. degree from California College of Medicine, 1962. Doctor Blumstein was a member of the Los Angeles County Medical Association.

⁂

Carlson, Frederick John, Walnut Creek. Died 1 December 1967 in Oakland of arteriosclerosis coronary arteries, aged 77. Graduate of Northwestern University Medical School, Chicago, Illinois, 1920. Licensed in California in 1920. Doctor Carlson was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Corr, Donald John, Riverside. Died 2 November 1967 in Loma Linda, aged 41. Graduate of Stanford University School of Medicine, Palto Alto-San Francisco, 1953. Licensed in California in 1953. Doctor Corr was a member of the Riverside County Medical Association.

⁂

Dwankowski, Carl, Norwalk. Died 30 November 1967 in Norwalk of cerebral hemorrhage and hypertension, aged 56. Graduate of Uniwersytet Jozfa Pilsudskiego, Warszawa, Poland, 1939. Licensed in California in 1946. Doctor Dwankowski was a member of the Los Angeles County Medical Association.

⁂

Fischer, Stanley Samuel, Oakland. Died 16 November 1967 in Oakland of arteriosclerotic heart disease, aged 61. Graduate of Washington University School of Medicine, St. Louis, Missouri, 1928. Licensed in California in 1930. Doctor Fischer was a member of the Alameda-Contra Costa Medical Association.

⁂

Friedman, Herbert Pincus, Jr., La Mirada. Died 14 November 1967 in Los Angeles of cardiac arrest, aged 48. Graduate of the University of Virginia School of Medicine, Charlottesville, 1944. Licensed in California in 1953. Doctor Friedman was a member of the Los Angeles County Medical Association.

⁂

Friedman, Martin I., Los Angeles. Died 2 December 1967 in Los Angeles of myocardial infarction, arteriosclerotic heart disease, aged 41. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1954. Licensed in California in 1955. M.D. degree from California College of Medicine, 1962. Doctor Friedman was a member of the Los Angeles County Medical Association.

⁂

Hardwig, Oswald C., Walnut Creek. Died 11 November 1967 in Walnut Creek of acute myocardial infarction, aged 59. Graduate of State University of Iowa College of Medicine, Iowa City, 1933. Licensed in California in 1963. Doctor Hardwig was a member of the Alameda-Contra Costa Medical Association.

⁂

Hartwig, Lucile Grosser, Los Angeles. Died 6 November 1967 in Los Angeles of combined metastases, aged 70. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1927. Licensed in California in 1927. Doctor Hartwig was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Haynes, Frank W., Arcadia. Died 22 November 1967 in El Monte of cardiac arrest and coronary arteriosclerosis, aged 93. Graduate of St. Louis University School of Medicine, Missouri, 1911. Licensed in California in 1921. Doctor Haynes was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Ickstadt, Albert, Jr., Coronado. Died 27 September 1967 in San Diego of bronchogenic carcinoma, aged 66. Graduate of Rush Medical College, Chicago, Illinois, 1927. Licensed in California in 1929. Doctor Ickstadt was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Levick, Alfred David, Los Angeles. Died 17 November 1967 in Los Angeles of metastatic malignancy to vertebra, aged 59. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1933. Licensed in California in 1943. Doctor Levick was a member of the Los Angeles County Medical Association.

Loughlin, Edward L., Frazier Park. Died 1 December 1967 in Los Angeles of lung cancer, aged 69. Graduate of St. Louis University School of Medicine, Missouri, 1929. Licensed in California in 1929. Doctor Loughlin was a member of the Los Angeles County Medical Association.

Mullen, Thomas Francis, San Carlos. Died 12 November 1967 in Portola Valley, aged 82. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1912. Licensed in California in 1927. Doctor Mullen was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Shea, Paul A., San Diego. Died 17 November 1967, aged 48. Graduate of Loyola University School of Medicine, Chicago, Illinois, 1944. Licensed in California in 1944. Doctor Shea was a member of the San Diego County Medical Society.

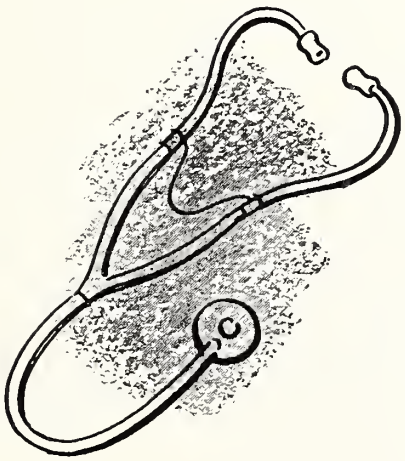
Way, Stuart C., San Francisco. Died 20 November 1967 in Palo Alto, aged 77. Graduate of the University of Louisville School of Medicine, Kentucky, 1919. Licensed in California in 1920. Doctor Way was a member of the San Francisco Medical Society.



Wilson, Francis N., Oakland. Died 13 November 1967 in Oakland, aged 49. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1944. Licensed in California in 1948. Doctor Wilson was a member of the Alameda-Contra Costa Medical Association.



Wilson, Robert O., Arcadia. Died 16 November 1967 in Arcadia of heart disease, aged 61. Graduate of Harvard Medical School, Boston, Massachusetts, 1933. Licensed in California in 1944. Doctor Wilson was a member of the Los Angeles County Medical Association.



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University of Colorado School of Medicine

DANIEL DEYKIN, M.D.
Assistant Professor of Medicine
Harvard Medical School

JAMES L. GODDARD, M.D.
Commissioner
Food and Drug Administration

CECIL HOUGIE, M.D.
Associate Professor of Pathology
University of Washington School of Medicine

TOD H. MIKURIYA, M.D.
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Center for Narcotics and Drug Abuse Studies
National Institute of Mental Health

JOHN A. OATES, M.D.
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Vanderbilt University School of Medicine

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GUEST SPEAKER: Michael B. Shimkin, M.D., Professor of Medicine and Assistant Vice-President for Research, Temple University Health Sciences Center, Philadelphia, Pennsylvania.

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RHEUMATOLOGY...RHEUMATOID ARTHRITIS...CANCER OF THE BREAST...CANCER OF THE LARGE INTESTINE...

Psychiatric Emergencies and Psychedelic Drugs

THURSDAY, FEBRUARY 1

Morning Session

RHEUMATOID ARTHRITIS

9:00—Clinical Definition and Epidemiologic Characteristics—Piero Mustacchi, M.D.

9:30—Vaseulitis, Protein Changes and Tests for Rheumatoid Arthritis—Wallace V. Epstein, M.D.

REALISTIC APPROACH TO DIAGNOSIS AND MANAGEMENT OF RHEUMATOID ARTHRITIS

10:30—The Point of View of the Internist—Ephraim P. Engleman, M.D.

11:15—The Contribution of the Radiologist—Howard L. Steinbach, M.D.

11:45—The Role of the Surgeon—William R. Murray, M.D.

12:15—Considerations on Radiotherapy—Theodore L. Phillips, M.D.

Afternoon Session

CANCER OF THE BREAST

2:15—An Overview of the Problem—Michael B. Shimkin, M.D.

3:15—When Do I Elect Radical Surgery—Maurice Galente, M.D.

3:45—How I Would Approach Primary Breast Cancer—Theodore L. Phillips, M.D.

4:15—Panel Discussion and Open Forum
Current Practices and Unresolved Questions
Moderator: Michael B. Shimkin, M.D.
Maurice Galante, M.D., Theodore L. Phillips, M.D., Nicholas L. Petrakis, M.D.

FRIDAY, FEBRUARY 2

BREAKFAST ROUNDTABLE DISCUSSIONS

8:00—Surgery and Radiotherapy of Cancer—Maurice Galante, M.D., Theodore L. Phillips, M.D.
Applied Immunology and Clinical Allergy—Wallace V. Epstein, M.D. and Piero Mustacchi, M.D.
Injection of Painful Joints and Bursae, Orthopaedie Surgery—William R. Murray, M.D.
Gout and Other Arthritides—Ephraim P. Engleman, M.D.
Anemia and Transfusion Practices—Nicholas L. Petrakis, M.D.
Problems of Investigations on Man—Michael B. Shimkin, M.D.

Problems of Pain Control—Stuart C. Cullen, M.D.

Radiological Diagnosis of Arthritis—Howard L. Steinbach, M.D.

Psychiatry, Psychedelic Drugs—Carroll M. Brodsky, M.D.

Morning Session

CANCER OF THE LARGE INTESTINE

9:30—**Radiologic Aspects**—Howard L. Steinbach, M.D.

9:50—**Surgical Problems**—Maurice Galante, M.D.

10:10—**Questions and Answers**

NEW KNOWLEDGE AND PRACTICAL IMPLICATIONS

10:30—**Cancer Chemotherapy**—Nicholas L. Petrakis, M.D.

11:00—**Endocrine Aspects of Cancer**—Michael B. Shimkin, M.D.

11:45—**Panel Discussion**
The Total Approach to the Cancer Patient
Moderator: Stuart C. Cullen, M.D.
Michael B. Shimkin, M.D., Nicholas L. Petrakis, M.D., Maurice Galante, M.D., Carroll M.
M.D., Maurice Galante, M.D., Carroll M.
Brodsky, M.D., and Theodore L. Phillips, M.D.

Afternoon Session

PROGRESS IN RHEUMATOLOGY

2:00—**The Spectrum of Spondylitis and Reiter's Disease**—Ephraim P. Engleman, M.D.

2:45—**The Increasing Family of Lupus and Lupus-Like Disorders**—Wallace V. Epstein, M.D.

3:30—**Questions and Answers**

4:00—CONCURRENT PANELS (you may attend the one of your choice)

A. Neoplastic Diseases of the Bone—William R. Murray, M.D. and Theodore L. Phillips, M.D.

B. An X-ray Clinic of Rheumatoid Disease—Ephraim P. Engleman, M.D. and Howard L. Steinbach, M.D.

C. Psychiatric Emergencies—Carroll M. Brodsky, M.D.

18th annual regional postgraduate institute

OJAI VALLEY INN Ojai Friday-Saturday March 1-2, 1968

WEST COAST COUNTIES

Presented cooperatively by West Coast Counties Medical Societies, University of California at Los Angeles School of Medicine and California Medical Association Committee on Continuing Medical Education. A 12-hour course.

HOST: Santa Barbara County Medical Society
Ventura County Medical Society
Regional Chairman: George J. Wittenstein, M.D.

INSTITUTE FEE: $20.00. For additional information contact Continuing Medical Education office, California Medical Association, 693 Sutter Street, San Francisco 94102. All California Medical Association members and their families are cordially invited to attend.

GUEST SPEAKER: C. Walton Lillehei, M.D., Lewis Atterbury Stimson Professor of Surgery and Chairman, Department of Surgery, New York Hospital—Cornell Medical Center.

PROGRAM THEMES:

BREAST CANCER...MILITARY MEDICINE...CORONARY INSUFFICIENCY...ADOLESCENCE AND THE DRUG PROBLEM...Computer Medicine...Contraception...Management of Rh Sensitized Pregnancies

FRIDAY, MARCH 1

Morning Session

BREAST CANCER

9:00—Introduction—Epidemiology—Lowell E. Irwin, M.D.

9:30—Radiology—Julius H. Grollman, Jr., M.D.

10:15—Surgical Treatment—C. Walton Lillehei, M.D.

10:45—Chemotherapy and Terminal Care—Lowell E. Irwin, M.D.

11:15—Panel Discussion—Question and Answer Session.

Afternoon Session

2:00—Military Medicine—Viet Nam—Brigadier General James A. Wier, MC

3:15—CONCURRENT WORKSHOPS

A 1. Contraception—Richard A. Bashore, M.D.

A 2. Management of Rh Sensitized Pregnancies —Richard A. Bashore, M.D.

B. Neurologic Complications of Cancer—Morton K. Rubinstein, M.D.

C. Computer Medicine—Baldwin G. Lamson, M.D.

SATURDAY, MARCH 2

Morning Session

EVALUATION AND TREATMENT OF PATIENTS WITH CORONARY INSUFFICIENCY

9:00—Introduction—Mark E. Winfield, M.D.

9:30—Radiology—Julius H. Grollman, Jr., M.D.

10:00—Medical Aspects—Mark E. Winfield, M.D.

10:45—Surgical Aspects—C. Walton Lillehei, M.D.

11:15—Panel Discussion—Question and Answer Session.

Afternoon Session

2:00—Adolescence and The Drug Problem—J. Thomas Ungerleider, M.D.

3:15—L.S.D.—Problems and Prospects
Video Tape—Contrasting views of the current uses and abuses of this fantastic chemical.

Health Careers

LET'S TAKE a hard look at the Health Careers numbers game. Between 1950 and 1965 the number of physicians engaged in the active practice of medicine in the United States increased 19 per cent, but the population increased 28 per cent. In 1950 the ratio was one physician to 974 persons, in 1965 it was one to 1,051.

There are 621,000 registered nurses (RN) now engaged in their profession in the United States—yet 21 per cent of hospital positions are unfilled, and many hospitals have closed some of their wards or in some places have substituted trained aides for RNs. Fifty thousand RNs are needed to fill positions now vacant. It is estimated we will need 850,000 by 1970, an increase of 229,000 in the next three years. We now have 19,500 nurse educators, and it is estimated we will need 10,500 more in three years just to *train* the needed nurses.

By 1970 the health career field will be the largest single field of occupation in the United States. Just as business, industry, science, the arts and the professions urge students to enter these fields of endeavor and depict attractively the returns connected with them, we must urge youth to enter a health career.

Your Woman's Auxiliary is aware of the problems facing Medicine; more important, we have been doing something about them. Every organized County Auxiliary in California has an active health career program. When an organization has 9,200 intelligent, determined women seeking the means to an end, it is a cogent force, indeed.

This past year we collected, through fund-raising efforts, over $82,400 for scholarships and loans. This brings the grand total over the years in California to almost two million dollars. More than a thousand students have been added to the health career team in the past four years by your Auxiliary's scholarships and loans.

This past year we sponsored 340 Health Career and Future Nurse Clubs in High Schools throughout the state. Twenty-eight counties had a Health Career Conference, reaching more than a hundred thousand people.

Our members spoke in schools, at PTA meetings, women's clubs, youth groups, for the press, radio and television. We sponsored spot ads for Health Careers on radio stations. We supplied pamphlets, books, charts, posters, pins and films.

We have many other activities which relate to Health Careers. These include various community service projects: sponsoring hospital auxiliaries, Candy-Striper* units for boys and girls 16 and over; and for younger boys and girls we have similar groups called the Band-Aids. We teach a comprehensive baby-sitting course. We sponsor medical self-help courses. We have legislative committees that are concerned with health bills on the state and national level. We have a rural health program to interest rural youth in health careers (through programs at 4-H, Future Farmers of America and booths at county fairs). We maintain a liaison with the Woman's Auxiliary to the Student American Medical Association to help recruit young physicians for rural areas. (Be apprised, by the way, that we find it more effective to convince the wife first!). We have baby-sitting services for women who want to study a health career but have a family at home.

We have sponsored glaucoma clinics, poliomyelitis clinics, tetanus clinics. We provide Meals on Wheels to the homebound. We collect drugs for needy hospitals overseas.

*The name comes from the candy-striped uniforms that many of the girls wear.

One County Auxiliary sponsored a medical secretarial course in the high school and purchased the dictaphone for class use. We organize Block Mothers for disaster preparedness, sponsor Homemaker Health Aide Service to release hospital and nursing home beds where possible, and train Volunteer Friendly Visitors to relieve loneliness of both patient and volunteer. We have just added a School Health Committee, whose chairman is an Auxiliary member who is also an M.D. While the function of this committee is primarily education and prevention, by its very nature it will stimulate interest in health careers at the elementary and junior high level.

Your Auxiliary has been interested in Health Careers for almost 40 years. For the last 15 years our program has been primarily aimed at recruitment, first for medicine and nursing and then for all health careers. We believe that we contributed substantially to the 50 per cent increase in recruitment in that span.

We are setting up programs to reach people of many orders and all ages—adults who have been trained but who have not been active in the recent past, returning military personnel, retired workers, persons who have been "automated" out of jobs, housewives, others. A special 9,200 doctors of medicine in California whose wives contributed to this labor of love, can look on this record with personal pride. I hope you are one of that number.

MRS. JOHN FITTIPOLDI, JR.
Health Careers Chairman



PUBLIC HEALTH REPORT

Lester Breslow, M.D., M.P.H.
Director, State Department of Public Health

Leprosy in California

LEPROSY IS NOT a major public health problem in California, but sporadic cases do occur, largely due to immigration from other states and adjoining as well as distant countries.

However, new cases in California residents who have never left the state are also detected through routine examination of contacts to patients with lepromatous leprosy.

Leprosy is only mildly contagious, and then usually after prolonged contact. Two major types are recognized: lepromatous leprosy, characterized by low host resistance and the presence of numerous bacilli, with involvement of skin, mucous membranes, eyes, peripheral nerves, and many internal organs; and tuberculoid, in which there is high host resistance, few or no bacilli, and only skin and peripheral nerve involvement. Patients with leprosy diagnosed in California show a great variety in ethnic origin. Among the patients registered with the Leprosy Service of the Public Health Service Hospital in San Francisco, the largest single ethnic group is Caucasians. Filipinos are next, followed by Mexicans. Some of these patients were born in the continental United States and never left the country.

The history of one patient with lepromatous leprosy is interesting from an epidemiologic point of view. He was born in Grand Rapids, Minnesota, and lived there long after the first symptoms of the disease, consisting mainly of sensory disturbances, appeared. When the local physician was unable to diagnose the disease, he went to one of the foremost medical institutions in the country, where his condition was diagnosed as syringomyelia. Although skin and eye manifestations appeared and the clinical manifestations became typical for leprosy, the disease was not recognized for years, because no physician considered the possibility of leprosy in a white man who had never left his native state.

How did this man acquire leprosy in Minnesota? The last remnants of the great leprosy epidemics of Europe persisted in the Scandinavian countries well into the 19th century. Immigrants brought the disease to Minnesota. At the turn of the century there were about a hundred cases of leprosy in that state. This man appears to have the last case of leprosy among the third generation descendants of the original immigrants.

This story illustrates another important point — the long delay between appearance of symptoms and correct diagnosis, due to the low index of suspicion for leprosy in this country. Leprosy is a great imitator and can simulate many diseases, especially those affecting the skin.* It can occur in persons of any race, and it can and does occur in men, women and children who have never left the continental United States. A thorough clinical evaluation may suggest the diagnosis, which should be confirmed by a histopathologic examination of a skin or nerve specimen obtained by biopsy.

In California two outpatient departments provide free diagnostic and treatment services for patients with leprosy, and consultative services for public health officers and private physicians. One is part of the Leprosy Service of the PHS Hospital in San Francisco and serves Northern California. The other is jointly operated by the University of Southern California Medical School, the Los Angeles County Department of Public Health and the Public Health Service. It is attached to the PHS Outpatient Clinic in San Pedro and serves Southern California. In addition to outpatient care, the Leprosy Service at the PHS Hospital in San Francisco offers inpatient care, and admits patients with leprosy for work-up and initiation of

*Fasal, P.: Leprosy Occurs Everywhere, GP 32:95-102 (Oct.) 1965.

treatment, for complications of leprosy, for intercurrent illnesses and operations and, also, to remove persons with communicable cases from contact with family members while prophylactic measures are carried out.

The Leprosy Service at the PHS Hospital in San Francisco is headed by Paul Fasal, M.D., who has been Consultant in Leprosy to the Department of Public Health, State of California since 1954. He was instrumental in initiating the ambulatory treatment of patients with leprosy in California. He started to treat selected patients in his office in 1953, and by 1960 had accumulated 15 patients. At this time the PHS decided to open a Leprosy Clinic at the PHS Hospital in San Francisco with Dr. Fasal as the director. Originally, the clinic was held twice monthly. It now has close to 200 registered patients and is held twice a week.

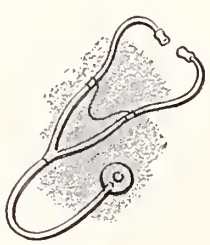
In 1966 a Leprosy Service was created at the hospital, with Dr. Fasal as chief. The Leprosy Service is responsible not only for the outpatient clinic, but for the inpatients who have leprosy (a recent census showed 16 patients), and for coordination of all consulting services. Consultation is available in internal medicine, surgery, neurology, orthopedics, ophthalmology and physical medicine. A leprosy research department has been established under Dr. Fasal's associate, Louis Levy, M.D., Ph.D., and various studies are in progress, using the mouse foot pad inoculation technique developed by Shepard.

In Southern California a leprosy clinic was opened in 1962 in The Good Hope Medical Foundation, Los Angeles, under the direction of Norman E. Levan, M.D., professor of dermatology at the University of Southern California, and Margaret Ann Storkan, M.D., associate clinical professor of dermatology at USC. In 1965 this clinic was transferred to the PHS Outpatient Clinic in San Pedro with Drs. Levan and Storkan as consultants. The clinic provides complete outpatient treatment of leprosy, with the clinic's other medical and dental services available to patients with leprosy. Patients may be admitted for short-term treatment at Los Angeles County General Hospital or at the PHS Hospital in San Francisco.

Early diagnosis is of paramount importance in the control of leprosy. If detected early, the disease usually responds well to drug therapy, but treatment must be adequate and continued for long periods. The drug of choice at present is 4, 4′-diaminodiphenylsulfone (dapsone), but one must watch for complications and for drug resistance. All contacts to patients with active lepromatous leprosy, especially family members, have to be examined, and prophylactic measures—BCG vaccination or chemoprophylaxis with dapsone, or both—might be needed. Close contact between patients with active lepromatous leprosy and children should be avoided.

In the occasional case where long-term stay in hospital is necessary, patients are referred to the PHS Hospital in Carville, Louisiana. This hospital has excellent facilities, particularly when major rehabilitative measures are necessary.

The work of Shepard, who succeeded in growing lepra bacilli in the foot pads of mice, has confirmed the effectiveness of chemotherapy and prophylaxis in animal experiments. Continued world-wide research promises even more effective methods for eventual control of leprosy.



NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

A gift of $487,200 from the Louis B. Mayer Foundation, to construct and equip the **Louis B. Mayer Medical Teaching Center** at the USC School of Medicine, was announced recently by the Foundation. The Center, which will have a 500-seat auditorium and 20 special teaching rooms, will be a part of the $2,375,000 complex of facilities for medical education planned for USC's 12-acre medical campus adjacent to the Los Angeles County General Hospital.

* * *

The City of Hope Medical Center is offering a one or two year fellowship, starting early in 1968, which provides clinical experience and opportunity for laboratory research in various aspects of **blood and neoplastic diseases of childhood.** Applicants should have completed at least a one year residency in pediatrics. A California license or eligibility is required. Salary, up to $9,000 a year, depends on qualifications. Details are available from Robert B. Rosen, M.D., City of Hope Medical Center, Duarte 91010.

* * *

Clinical research **fellowships in oncology and cancer chemotherapy** are now available at the University of Southern California School of Medicine, under sponsorship of the National Cancer Institute. The fellowships are of one or two years' duration, and are available immediately and 1 July 1968. If desired, the fellowships can include a three-month rotation on the Hematology Service of Los Angeles County General Hospital. A year of fellowship can substitute for a year of residency for board eligibility. The stipend for the first year is $6,000, of which $3,600 is tax-free, and additional allowance is made for dependents and advanced status.

Applicants should have completed at least one year of approved medical residency and be eligible for a California license. They should send a brief resume to David C. Stolinsky, M.D., USC School of Medicine, 2025 Zonal Avenue, Los Angeles 90033.

* * *

Quality in health care will be the theme of the 1968 National Health Forum to be held March 15 to 17 at the Statler-Hilton Hotel in Los Angeles. The Forum will bring together leaders in the health professions and related fields to assess standards and procedures for assuring quality in health care services and to consider proposals for strengthening these standards and procedures. Dr. Samuel R. Sherman, San Francisco, is chairman of the Planning Committee for the 1968 Forum, the 16th in a series sponsored by the National Health Council, a federation of 75 voluntary and professional societies in the field of health.

Dr. Christian N. Barnard, the South African surgeon whose two human heart transplantations have made medical history, will give American heart specialists a progress report on his operations 2 March at the annual meeting of the American College of Cardiology in San Francisco. The ACC meeting is scheduled for February 28 to March 3 at the San Francisco Hilton.

Dr. Barnard will address College members at 2 p.m., opening the Saturday, 2 March, session of "Progress Reports in Cardiology," one of the most popular sections of the annual meetings. Immediately following his report, Dr. Michael E. DeBakey, Houston, who implanted a partial "artificial heart" in 1966, will make a report of his more recent work.

GENERAL

Two regional scientific meetings under the auspices of the **American College of Physicians** will be held in California in February, one in Monterey, the other in Palm Springs. The **Monterey meeting** will be held February 16 to 17 at the Mark Thomas Inn, and the **Palm Springs meeting** February 23 to 25 at the El Mirador Hotel. Further information on the Monterey meeting may be obtained from Roberto F. Escamilla, M.D., 897 Hyde Street, San Francisco 94109; and on the Palm Springs meeting from W. Philip Corr, M.D., 3660 Arlington Ave., Riverside 92506.

* * *

At the meeting of the board of trustees of the **California Society of Physical Medicine and Rehabilitation,** the following officers were elected: President, Dr. Bernard F. Michela, Long Beach; vice-president, Dr. Alfred C. Hughes, Mountain View; secretary-treasurer, Dr. Laszlo Ambrus, Harbor City.



The Physician's BOOKSHELF

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 66 of the Advertising Section.

CERVICAL SPONDYLOSIS—And Other Disorders of the Cervical Spine—Edited by Lord Brain, D.M., LL.D., D.C.L., D.Sc., F.R.C.P., F.R.C.S., F.R.C.O.G., F.R.S., F.F.R., Consulting Neurologist to the London Hospital and Consulting Physician to the Maida Vale Hospital, and Marcia Wilkinson, D.M., F.R.C.P., Consultant Neurologist, Elizabeth Garrett Anderson Hospital and the Hackney and Queen Elizabeth Group of Hospitals; Director, Regional Neurological Unit, Eastern Hospital, Hackney, E.9. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 232 pages, $10.00.

The reviewer looked forward to this book with a great deal of anticipation. He must admit to a degree of disappointment. Cervical spondylosis is a common and clinically troublesome problem. Despite this, it remains a poorly recognized and understood one. It often mimics other disease, may go unrecognized or misdiagnosed and be poorly or improperly treated. One would hope that this book would help correct this situation by clarifying the clinical picture, the examination of the patient and his treatment. It does this but not to the degree or with the clarity that is needed.

The book contains nine chapters, six by the editors, Brain and Wilkinson, and three by other contributors. The chapter on history and the ones on pathology and radiology are good. The latter is especially noteworthy, being useful and well done with a good discussion of how to evaluate the x-ray changes of cervical spondylosis. The chapter on anatomy is complete—in fact, more so than most readers will desire. It is especially useful for reference.

The clinical chapters are the disappointment. The ones on symptomatology and diagnosis fail to come through with a clear clinical picture except in the discussion on myelopathy, which is well done. Little is said about several aspects of cervical spondylosis: its mimicry of coronary artery disease and how to differentiate the two (no small task at times); its production of the posterior cervical sympathetic syndrome which may give vague and yet clinically troublesome symptoms. The examination of the patient is barely mentioned and yet much that is clinically useful and little appreciated could be said about this. The chapter on medical treatment is standard but barely mentions vertical cervical traction, which is often the most rewarding way of treating these patients in addition to being a helpful technique in making the diagnosis. Surgical treatment is admittedly a difficult problem, with the approach and choice of procedures open to honest debate. The discussion of this brings in the current thinking regarding surgical approaches and therapy. It brings out well the fact that cervical spondylosis is a difficult problem to help surgically.

Much of the pertinent literature is reviewed or referred to but the clinical chapters are inbred and have limited reference to the work of other authors. The interesting and useful monograph by David Davis, "Radicular Syndromes—With Emphasis on Chest Pain Simulating Coronary Disease," is not mentioned. Other articles adding to the clinical picture are not mentioned.

Unfortunately, nothing is said about the ways one can help prevent the development of significant cervical myelopathy by anticipating the problem in high-risk patients. An entire chapter could be built around this subject.

In summary, the book has excellent parts but it will not give the clinician help and guidance to the degree that it could or should and it will be a disappointment to those who are familiar with the field. Nonetheless, it makes a real contribution to this problem and should be selectively read by those not well acquainted with cervical spondylosis.

PHILIP R. CALANCHINI, M.D.

* * *

THE PEDIATRIC PATIENT 1967—Coordinating Editor Sarah R. Gustafson, Ph.D., Director, Department of Medical Literature, Hoffman-La Roche Inc., Nutley, N. J.; and Consulting Editor David Baird Coursin, M.D., F.A.A.P., Director of Research, Research Institute, St. Joseph's Hospital, Lancaster, Pennsylvania. J. B. Lippincott Company, East Washington Square, Pa. (19105), 1967. 272 pages, 92 figures, $7.00.

This is the fifth annual edition of this publication which is sponsored by the Hoffman-La Roche Company. A copy of this book is provided free to almost every pediatrician by Hoffman-La Roche and the book is usually available to other physicians on request. The editors attempt to give a fairly comprehensive review of one or two subjects and a much briefer report on a dozen or so other topics of current interest. The references are quite up to date, and in addition to standard medical journals, they include reports given at recent medical meetings and information which has appeared in the pages of *Medical World News* and several of the medical newspapers.

This year's volume contains six chapters. The three topics selected for a review in depth are Computers in Clinical Medicine, Pediatric Cardiology and Childhood Speech and Reading Disorders. The remaining chapters deal with selected topics in Dermatology, "New Pathogens" and "Miscellany in Brief." The last chapter is miscellany indeed dealing with such diverse topics as Interferon—A Decade of Progress, Intensive Care Equipment for Newborns, Compulsory Screening for PKU and many other topics.

These are apparently the reports, papers and talks which appeared to be of greater interest to the editors.

This volume is somewhat reminiscent of the *Year Book of Pediatrics* but it is not as comprehensive as the latter and it does not contain the editor's incisive and critical comments on the papers being reported. The book is certainly well worth leafing through to sample a wide variety of material, and having done that, I am sure that many readers may wish to go back and give their careful attention to several areas of the book which might capture their interest.

MOSES GROSSMAN, M.D.

California Medicine

Peritoneal Dialysis in Chronic Renal Failure

DAVID N. EDELBAUM, M.D., ALBERT SOKOL, M.D., SANFORD GAYNOR, M.D., AND MILTON E. RUBINI, M.D., *Los Angeles*

■ *The long-term results of intermittent peritoneal dialysis in long-term treatment of renal disease have yet to equal those of intermittent hemodialysis. However, further exploratiou and refinement of this technique is justified.*

Performed in acute stages of disease, both peritoneal dialysis and hemodialysis relieve the symptoms of uremia and specifically "buy time" for the patient so that proper medical or surgical therapy may be instituted. In acute situations, peritoneal dialysis is the procedure of choice, and is an important adjunct to more conventional treatment for chronic renal disease. It may be useful sometimes even in chronically hemodialyzed patients—for example, when the hemodialysis cannula for one reason or another is inaccessible because of clots, replacement, or infection. It is especially valuable when the hemorrhagic complications of uremia contraindicate hemodialysis treatment.

Its use in chronic uremia remains sharply limited in time, but for brief periods chronic peritoneal dialysis appears to be a reasonably satisfactory means of prolonging life while awaiting homotransplant or decision for maintenance hemodialysis therapy.

PERITONEAL DIALYSIS is widely used in the treatment of acute renal failure, intoxication and intractable edema. In chronic renal failure it is indicated for brief periods of treatment of acute biochemical deterioration. Although protracted chronic treatment by this method has also been attempted, success has been limited.[1,2,5,9,13,14,16] This communication deals with the indications for the use of peritoneal dialysis in acute episodes of *chronic* renal disease and reports experience with intermittent peritoneal dialysis in the chronic management of renal failure.

From the Medical Service, Wadsworth Hospital, and Research, Veterans Administration Center, Los Angeles, and Department of Medicine, UCLA School of Medicine, Los Angeles.

Supported in part by U.S. Public Health Service grants TI AM 5383 and RO1-AM 08642.

Submitted 3 August 1967.

Reprint requests to: Metabolism Section, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevards, Los Angeles 90073 (Dr. Rubini).

Acute Phases of Chronic Renal Failure[3,9]

In addition to the vague generalized symptom complex called "uremia," patients with chronic

uremia may enter the hospital acutely symptomatic with cachexia, severe anemia, acidosis, edema and congestive heart failure. The correction of these disorders is often difficult, and therapy must be precise because of the lack of compensatory renal adjustments. Deficits may be more readily treated than surfeits. Thus, the physician can give saline solution to replace water and salt deficits; he can give alkali to correct acidosis. Treatment of abnormalities caused by surfeits is more difficult, as diuretics are often ineffective and he cannot depend upon augmenting renal excretion to correct accumulated excess. Severe anemia sometimes can be corrected only at the risk of precipitating pulmonary edema. Frequently, one is confronted by a severely uremic patient in whom the mechanism of acute decompensation is obscure, or in whom multiple interrelated physiologic distortions are present. At best, the therapy of the deteriorated uremic patient is complex, difficult, expensive and protracted. It is in these acute circumstances that peritoneal dialysis finds its greatest application in patients with chronic uremia. The following is a case in point.

CASE 1.—The patient was a 44-year-old, white man who had had proteinuria of moderate degree since 1942. He had pulmonary tuberculosis treated with pneumothorax in the 1940s. In 1956, following hemorrhage from a hiatus hernia, he was discovered to be mildly azotemic, but was asymptomatic. In August 1965, following complaints of easy fatigability, he was discovered to be anemic and azotemic, and in January 1966 his blood urea nitrogen (BUN) was 156 mg per 100 ml and creatinine was 9.6 mg per 100 ml. He was admitted to another institution where the diagnosis of chronic glomerulonephritis was made. He received several blood transfusions and a sharp restriction of salt intake was prescribed because of mild hypertension. His clinical condition continued to deteriorate.

He was admitted to the Wadsworth VA Hospital 11 March 1966 in what was considered "terminal uremia." He was anorectic and nauseated; the skin was deeply pigmented with excoriations and "frost"; generalized hyperirritability was evident. Serum creatinine on admission was 19.5 mg per 100 ml and BUN 250 mg per 100 ml; sodium was 118 mEq, chloride 88 mEq, potassium 5.3 mEq and carbon dioxide 10 mEq per liter. Uric acid was 14 mg per 100 ml. The patient was severely anemic. In spite of salt and water replacement, he remained severely ill with itching, nausea, vomiting and severe weakness. Peritoneal dialysis was carried out, with immediate but moderate improvement in symptoms. Dialysis was performed again two days later and decided biochemical and clinical improvement followed. On subsequent study, the patient was found to be a "renal salt-waster." On a daily intake of 10 the serum creatinine remained stable between 8 and 9 mg per 100 ml. A percutaneous renal biopsy was performed and changes consistent with chronic pyelonephritis were demonstrated. Repeated urine cultures were negative for pathogenic organisms.

The patient was discharged 2 May 1966 and was observed as an outpatient. A modified Giovannetti-Giordano dietary regimen,* with salt supplementation, was prescribed. Gradually the patient became hypertensive and congestive heart failure and anemia developed. Within six months the serum creatinine had reached 22.5 mg and the BUN was 139 mg per 100 ml, but for several months at least the patient was able to lead a fairly normal and not too uncomfortable life. (See Chart 1.)

He was readmitted to Wadsworth VA Hospital because of uremia and hyperkalemia, which did not respond to conservative measures. On 13 January 1967 peritoneal dialysis was carried out again and biochemical and clinical improvement promptly followed. Again the patient was discharged for regular observation as an outpatient but his clinical condition deteriorated rapidly and he required further peritoneal dialysis to sustain life.

On 2 April 1967 he had renal homotransplantation of a cadaver kidney. This had to be removed three days later because of hemorrhage and fracture of the renal cortex. He was successfully maintained on chronic intermittent hemodialysis until a successful retransplantation was done on 3 June 1967.

Peritoneal dialysis offers a practical "shortcut" to the temporary therapy of a patient with chronic uremia. As it offers no permanent resolution to the underlying pathologic processes, its use should be limited to acute symptomatic therapy. The patient's family should be aware of the limitation of such therapy, lest symptomatic improvement engender false hope of cure.

Peritoneal dialysis not only helps make the patient more comfortable, but it may bring a useful

*The low protein is limited to essential amino acids.

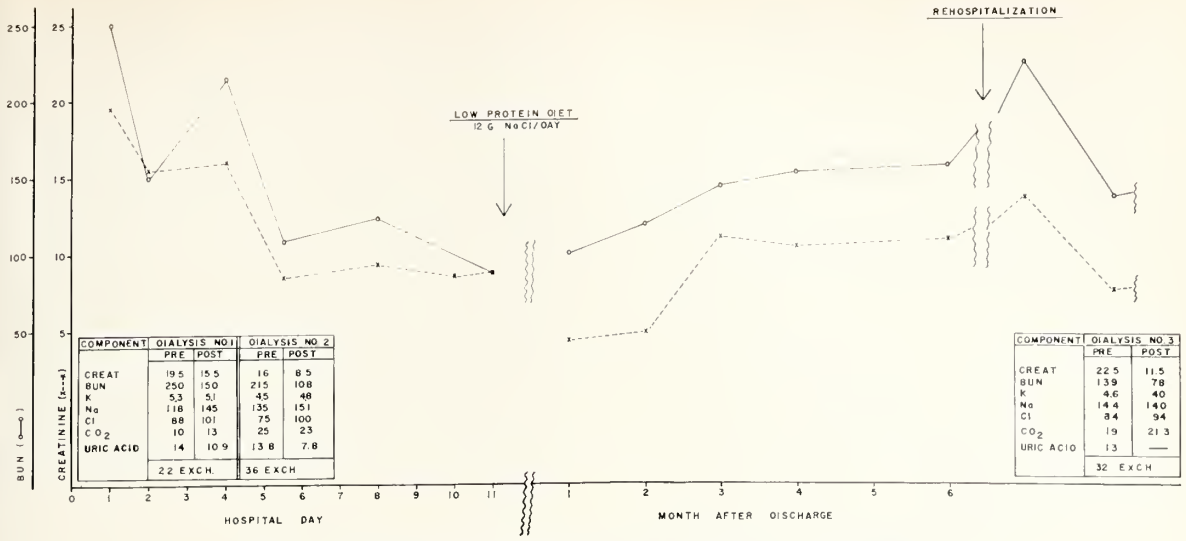


Chart 1.—Clinical course of patient in Case 1 before transplantation.

interval that can be used for critical diagnostic and prognostic studies. Complications that may have exaggerated the uremic state may be defined and alleviated. Such complications as acute pyelitis superimposed upon chronic pyelonephritis; salt and volume depletion as a result of injudicious use of diuretic drugs, salt restriction, or protracted vomiting; acute surgical crisis; and superimposed exogenous intoxications—any of these may respond readily to combined acute peritoneal dialysis and appropriate therapy. And once homeostasis is restored, a compensated state compatible with many months or even years of useful life may be reestablished. In addition, peritoneal dialysis may be useful to prepare a uremic patient with an unknown underlying renal disease for renal biopsy that will help in deciding the future course of action (Table 1).

Chronic Therapy in Chronic Renal Failure

Although extracorporeal, intermittent hemodialysis has been shown to be biochemically much more effective than peritoneal dialysis, various limiting factors such as large capital investment, long-term expense and the need for the establishment of special units have led physicians to attempt the maintenance of uremic patients by the simple technique of repeated peritoneal dialysis (Table 2). There are several reports concerning the long-term maintenance of such uremic patients with repeated peritoneal dialysis.[5,6,10-13,18] An illustrative case follows:

Case 2.—A 49-year-old white man was transferred 16 November 1963 from a U.S. Navy Hospital to Wadsworth VA Hospital with a diagnosis of hypertension and the nephrotic syndrome. He had a history of edema and shortness of breath of a month's duration. He had had three episodes of renal calculi between 1947 and 1957, and a 50 per cent sub-total gastric resection for peptic ulcer in 1963.

On physical examination the patient appeared chronically ill, was pale, hypertensive and edematous. Laboratory findings showed pronounced azotemia. Percutaneous renal biopsy revealed chronic "end-stage" glomerulonephritis. On 21 November, 1963, the first of a series of peritoneal dialysis procedures was done and on 10 December a peritoneal access "button" was implanted. Shortly thereafter, the cultures of peritoneal fluid became positive for a coagulase-positive staphylococcus Aureus which could not be eradicated with antibiotic therapy. However, clinical signs and symptoms of peritonitis were absent. Peritoneal dialysis was done a total of 60 times, about twice a week, between 10 December 1963 and 18 August 1964. Although

TABLE 1.—*Frequent Indications for Acute Peritoneal Dialysis in Chronic Renal Failure*

- Acute exacerbation of the underlying chronic disease.
- Intercurrent infection.
- Intractable edema.
- Acidosis and hyperkalemia.
- Massive salt and water overload.
- Preparation for renal biopsy or elective surgical procedure.

TABLE 2.—*Advantages and Disadvantages of Peritoneal Dialysis as Compared to Hemodialysis*[4,17]

ADVANTAGES:

- Available in any hospital.
- Simple; no need for specially trained personnel, special equipment, blood transfusions.
- Avoids hazards of hemodialysis; such as change in blood volume, transfusion reaction, over-heparinization, hemolysis, clotting.
- Slow but effective restoration of blood chemistry toward normal; better tolerated by severely uremic patients.
- Efficient removal of excess body water and salt.
- Minimal disturbance of critically ill patients.

DISADVANTAGES:

- Recurrent need for paracentesis.
- Danger of viscus perforation or hemorrhage.
- Infection and peritonitis.
- Limited biochemical control of uremia.
- Protein depletion with recurrent usage.
- Poor acceptance by the patient—pain and discomfort.
- No significant cost advantage over hemodialysis.

survival was substantially extended, the patient remained chronically ill and was out of the hospital for only brief periods. His clinical course throughout the long period in hospital was marked by progressive inanition and clinical deterioration, despite good control of biochemical abnormalities by peritoneal dialysis. He became severely anemic and had frequent episodes of hyperkalemia following dietary indiscretions.

An 20 August 1964, he received a cadaver kidney transplant from a patient who died of cancer of the lung. The transplanted kidney functioned well, and by the end of 1964 the patient's hematocrit had risen nearly to normal and creatinine clearance was stabilized at 45 ml per minute. The patient's condition was much improved and he was able to go home. Signs attributed to rejection were noted 30 December 1964, and biopsy of the homotransplant revealed apparently metastatic, poorly differentiated carcinoma involving the renal medulla and adjacent lymph nodes. The tumor was morphologically similar to the pulmonary carcinoma which was the cause of death of the kidney donor. The patient's clinical condition rapidly deteriorated and he died 24 January 1965.[7]

This case illustrates that it is possible to maintain life for protracted periods by intermittent peritoneal dialysis even in oliguric patients.

Repeated peritoneal dialysis at weekly or biweekly intervals was offered to 13 such oliguric patients who had insufficient renal function to sustain life, and whose survival therefore could be directly attributable to treatment. All of these patients had creatinine clearances of less than 5 ml per minute and were severely incapacitated by their disease. Several designs of indwelling conduits were used, but as infection occurred in each instance, an intermittent puncture technique was substituted, except for several who were transferred to maintenance hemodialysis or were offered renal transplantation.

All the oliguric patients on chronic peritoneal dialysis died within nine months, usually of infection and inanition. Several died suddenly, probably of acute arrhythmia secondary to hyperkalemia. Very few of the patients maintained on chronic intermittent peritoneal dialysis were satisfactorily rehabilitated.

In addition to these patients to whom a formal and rigid program of repeated peritoneal dialysis was offered, some 30 patients symptomatic with uremia who were not oliguric and whose disease was less advanced, were offered adjunctive repeated therapy. In these instances dialysis was performed electively when biochemical or clinical conditions deteriorated or oliguria supervened, and the interval between dialysis procedures varied. In the majority of cases, the interval progressively shortened; even with weekly dialysis the clinical state deteriorated and eventually dialysis was performed twice a week. Survival for more than four months was unusual. In a few instances, however, there was a substantial improvement after the first few dialysis procedures, and treatment could be deferred for protracted periods. While such cases were a distinct minority, in five of six patients with polycystic renal disease, correction of an acute decompensated state resulted in a significant clinical remission lasting from weeks to months before dialysis was needed again. That such progressive oli-

TABLE 3.—*Summary of Results of Chronic Intermittent Peritoneal Dialysis*[4,12]

1. All patients lost weight. Hypoalbuminemia developed in many. Protein losses up to 100 grams per dialysis were noted.
2. Half of patients had progressive and incapacitating peripheral neuropathy.
3. Hypertension was relatively easy to control as ultrafiltration was facilitated.
4. Hyperkalemia episodes were frequent. Biochemical control, especially of uric acid and phosphate, was grossly inadequate.
5. Clinical improvement was brief, and chronic illness was usual. Rehabilitation potential appeared extremely limited.
6. Infection eventually occurred in all instances.

guria did not develop in such patients would seem significant (Table 3).

New Approaches to Use of Peritoneal Dialysis in Maintenance

Several investigators have reported encouraging success with the use of a filter system which can prepare sterile, pyrogen-free dialysate at the bedside, and they have utilized various techniques of automatic cycling of dialysis fluid. Techniques for continuous peritoneal dialysis and the attainment of high exchange rates considerably increased the clearance of BUN and creatinine. For the time being, however, the use of these methods is still investigational and is restricted to a few institutions.[8,15]

REFERENCES

1. Boen, S. T.: Peritoneal Dialysis in Clinical Medicine, Charles C Thomas, Springfield, 1964.

2. Burns, R. O., Henderson, L. W., Haber, E. B., and Merrill, John P.: Peritoneal dialysis—Clinical experience, New Engl. J. Med., 267:1060-1066, 1962.

3. Gutch, C. F., Stevens, S. C., and Watkins, F. L.: Periodic peritoneal dialysis in chronic renal insufficiency, Ann. Int. Med., 60:289-296, 1964.

4. Palmer, R. A., Maybee, T. K., Henry, E. W., and Eden, John: Peritoneal dialysis in acute and chronic renal failure, Canad. Med. Assoc. J., 88:920-927, 1963.

5. Schumacker, R. R., Ridolfo, A. A., and Martz, B. L.: Periodic peritoneal dialysis for chronic renal failure, Ann. Int. Med., 60:296-305, 1964.

6. Schupak, E., Constantine, L., Hampers, David, Prager, Wayne, Poulos, Ann, and Kushner, Daniel S.: Peritoneal dialysis in chronic renal failure, Am. J. Med. Sci., 247:263-267, Mar. 1964.

7. Cohen, H.: A clinical evaluation of peritoneal dialysis, Canad. Med. Assoc. J., 88:932-938, 1963.

8. Lasker, Norman, McCauley, Eileen P., and Passarotti, Carol T.: Chronic peritoneal dialysis. Trans. Am. Soc. Artif. Int. Organs, 12:94, 1966.

9. Proceedings of the European Dialysis and Transplant Association, International Congress Series No. 103, Excerpta Medica Foundation, Amsterdam, 1964, 1965.

10. Proceedings of the Working Conference on Chronic Dialysis, University of Washington, Seattle, 1964.

11. Rubini, M. E., Sokol, A., Edelbaum, D. N., Gaynor, S. H., and Schneiweiss, R.: Chronic peritoneal dialysis—An evaluation of 45 patient-months of experience, Clin. Res., 13:115, 1965.

12. Vertes, V., Harris, Allan, and Lee, D. Y.: The treatment of chronic renal failure with periodic peritoneal lavage, JAMA, 200:97, 1967.

13. Martin, D. C., Rubini, Milton, and Rosen, Victor: Cadaveric renal homotransplantation with inadvertent transplantation of carcinoma, JAMA, 192:752-754, 1965.

14. Miller, J. H., Gipstein, R., Margules, R., Schwartz, M., and Rubini, M. E.: Automated peritoneal dialysis: Analysis of several methods of peritoneal dialysis, Trans. Am. Soc. Artif., 12:98-105, 1965.

15. Shinaberger, J. H., Shear, L., and Barry, K. G.: Increasing efficiency of peritoneal dialysis: Experience with peritoneal-extracorporeal recirculating dialysis, Trans. Am. Soc. Artif. Int. Organs, 11:76-82, 1965.

16. Stevens, R. E., Baskin, Sidney, Greene, James A., and Weller, John M.: Peritoneal dialysis in the management of chronic renal failure, JAMA, 190:1128-1132, 1964.

17. Stewart, J. H., and Neal, F. C.: Dialysis: A comparison of the efficiency of peritoneal dialysis with the artificial kidney, Med. J. Austr., 2:210, 1966.

18. Gordon, S., and Rubini, M. E.: Protein losses during peritoneal dialysis, Am. J. Med. Sci., 253:283-292, 1967.



Chronic Renal Disease

Some Sociological Aspects of Dialysis and Transplantation

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■ *Each year in California more than two thousand persons die of renal disease. Chronic uremia formerly was considered to have a hopeless prognosis. Recently the development of two procedures, chronic maintenance hemodialysis and renal homotransplantation, has offered substantial hope for the salvage of patients who otherwise would die of uremia.*

RENAL DISEASE was listed as the cause of death of 23,773 persons in the United States in 1962 and of 24,697 in 1964.[1-3] Almost one-half of these deaths were due to chronic nephritis, one-third to urinary tract infection. In addition, renal insufficiency was undoubtedly a major causative factor in death in a number of other diseases in which renal complications were not officially recorded, notably hypertension, diabetes and septicemia. The National Kidney Foundation has estimated that more than a hundred thousand deaths a year result from or are related to diseases of the kidney. In young adults, kidney disease is one of the major causes of death (Table 1). It is estimated that more than three million Americans have unrecognized and undiagnosed infection of the kidneys and are, therefore, susceptible to a substantial risk of progressive and irreparable loss of functioning renal mass.

"End-stage" renal disease is the final outcome of many diseases of different origin affecting the kidney, including glomerulonephritis, pyelonephritis, nephrolithiasis, various vascular diseases, diabetic glomerulosclerosis, gout and many other less common entities. In a large proportion of cases these diseases are chronic processes which may lead to progressive insufficiency of renal function that results in a chronic illness (nonspecifically called "uremia") due to chemical imbalance and inadequate capability to maintain homeostasis. Uremia is manifested by progressive weakness and a variety of symptoms involving the central nervous system, heart, gastrointestinal tract and skin. A long period of chronic debility often precedes frank physical incapacity, and anemia and hypertension usually develop. Symptomatic therapy then is interposed in an effort to retard or lessen the progressive uremia of advanced renal disease, but in many patients the underlying renal disease is not treatable and often the success of conservative treatment is temporary. Until recently the prognosis was hopeless for patients with chronic uremia and there was increasing infirmity during the last few months or years.

The bleak outlook for chronic uremia has recently been modified by the development of two procedures—hemodialysis and kidney transplantation. Both are the outgrowth of long preliminary studies. Hemodialysis was first attempted by Abel, Roundtree and Turner in 1913, but was essentially unsuccessful until Kolff reported his work in 1946.

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TABLE 1.—*Comparative mortality due to selected chronic diseases* (Per cent mortality by age groups)*

	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64
Diabetes mellitus§	12	15	15	11	10	10	11	13	13
Hypertensive disease†	5	10	15	19	21	22	23	22	23
Kidney diseases	30‡	25‡	25‡	18	15	13	11	10	8
Neurological conditions, excluding vascular	25	21	20	13	11	8	6	5	4
Rheumatic heart disease	20	20	25	22	20	18	15	12	8
Stroke (cerebral embolism, hemorrhage, and thrombosis)	8	9	13	16	22	29	34	39	44

*Source: Vital Statistics of the United States, 1962.

†Of these individuals, an average of 19 per cent had known kidney involvement.

‡This predilection of kidney disease for age groups 20-34 (at a time when they are heads of young households) creates a greater sociologic impact than diseases whose major incidence is in older individuals whose families have grown.

§While approximately one-third to one-half of individuals dying of diabetes have important renal involvement, the percentage of diabetic deaths caused directly by kidney disease is controversial. Joslin has estimated that (in 1950-57) 10 per cent of diabetic deaths were due to renal disease.[4]

Repeated treatment by the technique of hemodialysis became possible in 1960 with the development by Scribner and his associates of a permanent indwelling arterio-venous cannula-shunt.

Kidney transplantation was first attempted in animals by Carrel in France and Ullman in Germany in 1902. Although surgical techniques were perfected, an immunologic rejection of the graft caused failure until 1954, when it was demonstrated that grafts between identical twins were technically feasible. The next major advance was the introduction in 1962 of the drug azathioprine, which, when given in association with prednisone, proved capable of preventing immunologic rejection of a kidney transplanted from a donor of the same species. Thus, in this decade several hundred people who would otherwise have died of uremia have been returned to active, productive lives.

The availability of methods for the treatment of an otherwise fatal disease imposes the obligation to provide as soon as possible the facilities for all patients who would benefit from such therapy. It becomes immediately apparent that a number of unique problems exist. Patients on chronic hemodialysis require an indefinite commitment to a program which is expensive both in materials and personnel time. Successful kidney transplantation is still too new to predict ultimate demands for later hospitalization, dialysis or retransplantation. It is a situation which requires massive long-range planning, but is subject to sudden changes in the success of transplantation, the efficiency of equipment, and the availability of personnel which would limit the accuracy of such long-range planning. There undoubtedly is the moral imperative to make available the facilities to treat all such patients who would benefit. In several countries whose laws imply that all citizens are entitled to optimum medical assistance under tax-supported programs, those considerations have immediate practical meaning. They have similiar significance in California, where many patients can qualify under the current Medi-Cal legislation.

An analysis of deaths from nephritic conditions in the State of California in 1960 is presented in Table 2. The overall death rate from nephritic conditions was 96 per million; of these approximately one-half occurred in the ages between 15 and 54 years, and it is likely that most suitable candidates for chronic hemodialysis and renal homotransplantation are to be found in this age group. Comparable data from England and Wales are also reported in Table 2. Professor Nils Alwall of Lund, Sweden, has made projections for dialysis requirements in his country, assuming that transplantation remains at a modest level of clinical investigation. His data indicate that in Sweden there are 88 new cases of renal failure per million population per year. He recommends that dialysis facilities be established on the basis of 40 new cases per million population per year. Similar projections from England suggest 20 cases per million per year should be expected, and the results of a survey in Southeastern Ontario, Canada, anticipate a caseload of 24 to 33 per million population per year.[5] While these figures show some variability they are all of the same general order of magnitude.

Costs of Treatment

Thus, available data indicate that approximately 1 per cent of all deaths are due to kidney failure. At current mortality figures this is approximately 100 patients per million population per year, or approximately 2,000 annually for the State of California at the present population level. It is not yet known what proportion of these will be suit-

TABLE 2.—*Death rates from nephritic conditions* (State of California 1960 population: 15,717, 204)†*

	Rate Million Per Age Group					
	Under 15	*15-24*	*25-44*	*45-54*	*55 or Over*	*15-54*
Males	14	22	43	127	437	56
Females	9	22	39	102	335	49
All	12	22	41	114	382	52

Mortality from kidney diseases in 1962 in England and Wales (1962 total population of England and Wales: 42,985,000)‡

	Rate Million Per Age Group		
	5-14	*15-49*	*50 or Over*
"Nephritis"§	0.9	17.1	61.1
Other kidney diseases	0.6	7.1	75.5
Totals	1.5	24.2	136.8

*Nephritic conditions comprise International Classification of Disease, Seventh Edition, groups 591-594, 600.0, 601, 603, 757.1.

†Source: State of California, Department of Public Health, Bureau of Chronic Diseases.

‡Adapted from Belding H. Scribner: Ethical Problems of Using Artificial Organs to Sustain Human Life. Trans. Amer. Soc. Artif. Organs, Volume 10, Pages 209-212, 1964 (Presidential Address).

§This classification is probably more rigid than utilized in Table 1.

able for dialysis or transplantation, but a reasonable estimate for the next ten years is that at least 500 patients per year might benefit substantially if treatment were available. As a minimum estimate, about 50 per cent of patients dying of renal failure are in the ideal age range for treatment and 50 per cent of these would definitely benefit. Present data are insufficient to predict the rate of attrition of patients receiving therapy, but data from Seattle, where a chronic dialysis program has been in effect for seven years, indicate that a five-year survival of 75 to 85 per cent may be anticipated. Data from the Wadsworth Hospital dialysis program[7] confirm the success of treatment. Of the 34 patients started on hemodialysis therapy at this hospital over the past four years, 82 per cent have survived (Table 3). Assuming a 5 per cent annual attrition and an intake level of 500 per year, at ten years there would be in California 3,875 patients being dialyzed. Even if present costs could be halved to reach $6,500 per patient, a minimum of $25,000,000 would be required annually. Furthermore, the requirement for facilities for application of dialysis therapy would continually increase until the rate of loss by death approximately equalled the rate of input of new patients needing treatment.

These estimates for the number of patients and the cost per patient are based on two extremely tenuous assumptions: (1) that our estimates for the frequency of treatable uremia are correct and only one in four would benefit from hemodialysis; and (2) that the cost of hemodialysis can, in fact, be brought down to the level of $6,500 per patient per year. The apparent success of home dialysis programs suggests an alternative which may make this cost estimate truly realistic. Further, it is at present impossible to estimate the effect of successful kidney transplantation upon the ultimate need for hemodialysis. Kidney transplantation is proving to be increasingly successful and its relationship to chronic dialysis should be apparent within five to ten years. It seems improbable that transplantation will ever supplant dialysis. More, it is probable that dialysis will be needed as an adjunct to all transplantation programs. Finally, it is to be hoped and anticipated that eventually methods will be developed which will arrest kidney disease before uremia develops. Recent developments suggest that this may not be impossible for many diseases which produce uremia. However, there are no definite evidences of immediate success in this direction, and prevention will not be of benefit for those who already have failure of renal function.

The most recent report of the Human Kidney Transplant Registry indicates that 65 per cent of patients receiving living related donor transplants and 39 per cent of patients receiving cadaver donor transplants will have at least one-year survival of graft function.[6] Examination of recent data from centers that have had considerable experience, including our own, suggests that these results exceed 75 per cent for living donor transplants and 50 per cent for cadaver donor transplants.[2,9,10] Currently patients are discharged about three weeks after transplantation. Very few of the complications have been such as to limit the normal activity of patients with successful transplant.

TABLE 3.—*Case load and survival rate on hemodialysis, Renal Service, Wadsworth VA Hospital (January 1963 through April 1967)*

Renal patient admissions	*Patients requiring definitive treatment‡*	*Selected for chronic hemodialysis program*	*Chronic hemodialysis patient-years*	*Patient survival on chronic hemodialysis*
2100	± 210	32	35	26*
		+ 2†		+ 2‡
		34		28 (or 82%)

*Includes nine subsequently receiving renal transplant.

†One patient on dialysis four months awaiting transplant; one being maintained for retransplant since rejection of first transplanted cadaver kidney one month post-transplantation.

‡Patients with advanced symptomatic uremia whose survival beyond a few months would not be ordinarily anticipated. How many might have benefited from chronic dialysis is uncertain.

The ultimate length of transplant function cannot be predicted. Table 4 summarizes the results of the UCLA-Wadsworth experience through December 1966. These data are comparable to data from other transplantation centers for each period, and can be considered relatively representative. Much of the improvement has been due to greater success in using living related donors. On the other hand, although the results with cadaver donors has been promising, successful results have been achieved in approximately 56 per cent of attempts since 1964, without significant improvement in the proportion of successes during this period. Of the last 20 patients with transplantations in this series using living donors, 16 are still alive and 14 have satisfactorily functioning grafts. Of 20 patients for whom cadaver donors were used, 11 are alive and have satisfactory renal function. It should be noted that these transplants were performed a minimum of six months ago. Twenty-eight of the first 54 patients have survived for longer than one year, although two have subsequently lost renal function and now require hemodialysis. Only one patient of the 34 who survived the first six months has subsequently died. An abrupt decrease in the mortality after the first three to six months has been noted in most centers, and after this point the attrition appears to be very comparable to that among patients on chronic dialysis, although the experience is much shorter.

Case Selection

It should be recognized at the outset that case selection represents only an expediency based on limited facilities and in no way represents an ultimate social policy to select those "worthy" of treatment. Hemodialysis requires the expenditure of much time and money and the energies and talents of a skilled medical team. Since the patient's life is "saved" with each treatment week-after-week, the medical team must take an interest not only in the preservation of his life but also in the quality of the life they have restored. As the number of patients successfully kept alive by chronic dialysis has increased, it has become obvious to all workers in the field that mere survival is not the sole criterion of optimum patient response. Sociologic, psychologic and economic effect upon the individual, his family and the community are probably as important in defining successful therapy as simple physiologic response.

How can the decision best be made as to which patient receives treatment? This decision has great social consequence since at present those who are not chosen for dialysis will die. The criteria used for making these decisions must be as lucid and as objective as possible, especially in programs supported by public funds. In general, an attempt

TABLE 4.—*Summary of kidney transplantation experience, UCLA and VA Center, Los Angeles**

		Initial Function		*Present Function*		*Alive†*	
Period	*Total*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*
1957-62	7	4	57	1	14	1	14
1963	9	5	56	2	22	2	22
1964	7	6	86	4	57	4	57
1965	18	17	94	9	50	11	61
1966	29	27	93	17	63	18	67
1957-66	70	59	84	33	47	36	51
1964-66	54	50	93	30	56	33	61

*Data as of June 1967, i.e., at least six months after transplantation.

†Includes patients alive, but requiring hemodialysis.

is made to select those patients who appear to have the best physical and mental potential to benefit from the treatment program and return to normal and productive lives. In general, this implies an emotionally stable adult with minimum extra-renal disease. The criteria for selection publicized by the Seattle group include: (1) a stable, emotionally mature adult under the age of 45 who is disabled by symptoms of uremia; (2) absence of long-standing and permanent complications, particularly coronary artery disease and cerebral vascular or peripheral vascular disease; (3) willingness and ability to cooperate in carrying out the prescribed medical treatment; (4) renal function which is stable or deteriorating slowly, since any residual function simplifies the therapeutic program.

Many observers have voiced concern as to whether selection for chronic dialysis should be made by medical criteria alone, or should embrace such social questions as the value of one man versus another in society.[8] If social values are important, shall a man's worth be measured by the contributions he makes when he is well, or by the burden he leaves behind when he dies? Who is to judge the value of an individual in society? A physician? A group of physicians? A lay committee? And what are the criteria of social worth? Are they the same in all individuals? Are they rigidly definable, or do they change in time? What is to be done with the patient who no longer can fulfill the criteria utilized in initial selection, be they medical or sociologic?

There is also the problem of an educated consent. Can the uremic patient whose thought processes are befuddled by his illness have an understanding of the obligations and requirements that chronic dialysis imposes? Can the family accept the economic, emotional and functional responsibilities of dialysis? The very concept of medical triage is difficult for many physicians to accept, let alone practice. Is sociologic triage less moral than medical triage?

Successful kidney transplantation obviously represents the ideal solution to the problem of irreversible renal insufficiency. The patients may become essentially well and free of physical and dietary restrictions. The cost of their maintenance is limited to periodic laboratory tests and medical reexaminations. Their greatest limitations are due to the hazards of the immunosuppressive therapy with the associated risks of infection, and to the possibility that eventually the transplanted kidney may fail, requiring retransplantation or dialysis. Yet, with increasing utilization of cadaveric kidneys, the same problems of case selection for chronic dialysis become pertinent and applicable to homotransplantation. On the whole, those who have seen both successful transplantation programs and equally successful dialysis programs generally believe that there is little question as to the superiority of transplantation. These patients do better and the management of them is less complex medically, socially and economically.

Relationship of Transplantation to Dialysis

For optimum application of transplantation it is necessary to have an active dialysis program for several reasons: (1) experience indicates that a patient whose condition is stabilized by a period of dialysis responds more satisfactorily to transplantation than one who has not been so prepared; (2) the limitations in availability of cadaveric kidneys usually make it necessary to carry out dialysis for a period of time until a donor kidney becomes available; (3) patients with transplants that do not function immediately, particularly cadaver transplants, require dialysis until renal function is established; (4) in a significant number of patients the transplant will fail, and these patients will require resumption of dialysis until an attempt at retransplantation is possible; (5) similarly, there may be eventual failure of function, even in patients who have had transplantation that was for a time successful, and dialysis will have to be resumed during the interim before retransplantation; and (6) some patients may be poor candidates for transplantation because of the presence of significant systemic disease yet could have significant and comfortable prolongation of life through hemodialysis.

At the Medical College of Virginia, where hemodialysis is intimately related to a major transplantation program, 160 hemodialysis procedures were carried out, before and after operation, in support of 63 transplantations from living donors. Fifteen patients required dialysis within two weeks of transplantation. In Cleveland, 45 renal allografts (cadaver donor) were performed in 40 patients. Each recipient required dialysis before transplantation, and the number of times the procedure was carried out in individual cases ranged from three to 143. After transplantation, five patients required no dialysis; each of the other patients required

from one to thirteen. In connection with a 69-patient transplantation experience in Denver, 247 dialysis procedures were performed, averaging 3.7 per patient. Living related donors were used in most cases in that series, and long delays before transplantation were avoided. Therefore, dialysis was post-surgical for the most part. Only two patients did not have dialysis.

An ideal program for the treatment of patients with kidney failure combines transplantation with dialysis. Dialysis by itself presents an almost limitless problem. If the potential number of patients in the United States who will need dialysis is projected at 20,000 per year, it is conceivable that within a decade more than 150,000 will be undergoing dialysis. It is probable that even with improvements in technique, most communities would find social and professional facilities extremely extended to support a program of this magnitude. On the other hand, to the extent to which transplantation is successful, patients can be removed from the dialysis program. Therefore, the number of new patients requiring dialysis annually would be reduced and the total number of dialysis procedures required might be held within reasonable limits. Most of the patients with transplantation failure who formerly died can now return to dialysis as a result of improved surgical and dialysis management. Thus, a trial of transplantation is no longer the same vital decision that it used to be for the patient on dialysis who often faced the fact that if transplantation failed he could not return to dialysis. Certainly, the social burden of chronic dialysis will be relieved to the extent the transplantation is successful. Thus, the two programs are mutually dependent and afford for the first time a realistic hope that a modest proportion of persons now dying of kidney failure will be restored to useful and comfortable lives in their homes and communities.

It is our belief that within the next few years the ethical and economic problems relating to the treatment of patients with chronic uremia will have been largely resolved. This will be due to technical improvements on one hand and increased resources on the other. The problem will then return to the more conventional one of choosing the best treatment for the individual patients.

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REFERENCES

1. Fishman, Linda K., Kidney Disease Branch, Bureau of Chronic Diseases, Public Health Service, U.S. Department of Health, Education, and Welfare: Personal communication.

2. Hume, D. M., Lee, H. M., Williams, G. N. M., White, H. J. O., Ferre, J., Wolf, J. S., Prout, G. R. Jr., Slapak, M., O'Brien, J., Kilpatrick, S. J., Kauffman, H. M. Jr., and Cleveland, R. J.: Comparative results of cadaver and related donor renal homografts in man, and immunologic implications of the outcome of second and paired transplants, Ann. Surg., 164:352, 1966.

3. Kidney Disease: A Guide for Public Health Personnel, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1384, November 1965.

4. Marble, A.: Chapter *in* Diseases of the Kidney, Strauss and Welt, Little, Brown and Company, Boston 1963.

5. Morrin, Peter A. F.: A survey of chronic renal failure in Southeastern Ontario, Canad. Med. Assoc. J., 94: 25 June 1966.

6. Murray, J. E., Barnes, B. A., and Atkinson, J.: Fifth report of the human kidney transplant registry, Transplantation 5:752, 1967.

7. Rubini, M. E., Wolfram, J. G., and Sokol, A.: An analysis of a Veterans Administration dialysis unit, Trans. Amer. Soc. Artif. Int. Organs, 12:376-385, 1966.

8. Schreiner, George E., and Maher, John F.: Hemodialysis for chronic renal failure. III. Medical, moral and ethical, and socioeconomic problems, An. Int. Med., 62: 551-557, 1965.

9. Starzl, Thomas E.: Experience with Renal Transplantation, W. B. Saunders Company, 1964.

10. Straffon, R. A., Stewart, B. H., and Kaiser, W. S.: The use of 94 cadaveric kidneys for transplantation—Clinical experience, Brit. J. Urol., 38:640, 1966.

The Repair of Large Incisional Hernias

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■ *An old technique for the repair of incisional hernias, but with the use of Marlex mesh instead of fascia lata, was used in eight cases, with good results for the limited time the patients have been observed. The operation involves the use of a multifingered sheet of Marlex mesh, a material with characteristics that make it ideal for repair of large hernias.*

MANY INCISIONAL HERNIAS have been successfully repaired by some variation of technique involving approximation and overlapping of the fascial edges of the defect. At times the use of a sheet of fascia lata or some prosthetic material has been added for reinforcement by the onlay method.

Two years ago a patient was referred to one of us (IAK) with an incisional hernia so massive that it seemed the usual methods of repair would fail. A search of the literature for a more reliable method disclosed an operation first described by Gallie[2] and more recently by Burton.[1] This procedure involves the use of a fingered fascia lata graft and appears to result in a repair of great strength. Since the use of fascia lata requires an additional operative procedure and because there is a limit to the amount available, it was decided to substitute Marlex® mesh which has established itself as an ideal prosthetic material. Marlex is readily available, easily sterilized and well tolerated in the presence of infection. It is easily handled and maintains its strength. Furthermore, it is non-reactive and therefore does not promote seromas or adhesion formation even when in direct contact with bowel.

Impressed with the simplicity of the procedure and the excellent repairs achieved we believed that this modification of the Gallie technique should be reported.

Technique

The previous scar is excised and the sac is exposed and opened. The excess sac and thinned out scar tissue is removed, delineating the strong fascial edges of the hernia defect. This peritoneal-fascial edge is then cleared for a width of 2 to 3 cm intraperitoneally and subcutaneously. A sheet of Marlex mesh slightly longer than the defect and at least 25 cm wide is selected. Strips about 2 cm wide are then cut from each side, leaving the center area intact as shown in Figure 1. If the fascial edges can be approximated, the intact portion of the implant need be only 4 cm wide. However, if the edges cannot be brought together, the center portion should be 4 cm plus the width of the remaining defect when the edges are maximally approximated with clamps as shown in Figure 2. The strips are then threaded on Gallie fascia needles and brought through the peritoneal-fascial layer from the intraperitoneal side about 2 cm from the edge of the defect, and about 3 cm apart, as shown in Figure 3. Figure 4 shows the completed insertion of the Marlex mesh. The strips are then tied, using four throws to the knot. Marlex sutures on smaller needles are used to suture the fascial edges between the tied strips as shown in Figure 5. It may be possible to bury the large knots of the

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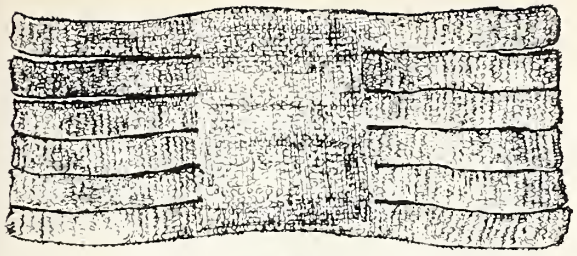


Figure 1.—Prepared Marlex mesh prosthesis.

Marlex strips between the edges of the fascia so they will not be palpable in a thin patient.

Since the wound is usually large and involves extensive dissection, a Penrose drain or suction-drainage tubing is inserted between the area of repair and the subcutaneous layer for a few days.

The use of such an inlay prosthesis is advantageous because of the simplicity of the introduction and the obvious strength of the repair. Furthermore, if the edges of the defect cannot be brought together, the Marlex mesh serves as a good fascial substitute without the possibility of the bowel insinuating itself between the prosthetic mesh and the abdominal wall, as might occur with the onlay method.

Case Material

We used this operation in seven patients with incisional hernias and in one patient with a defect

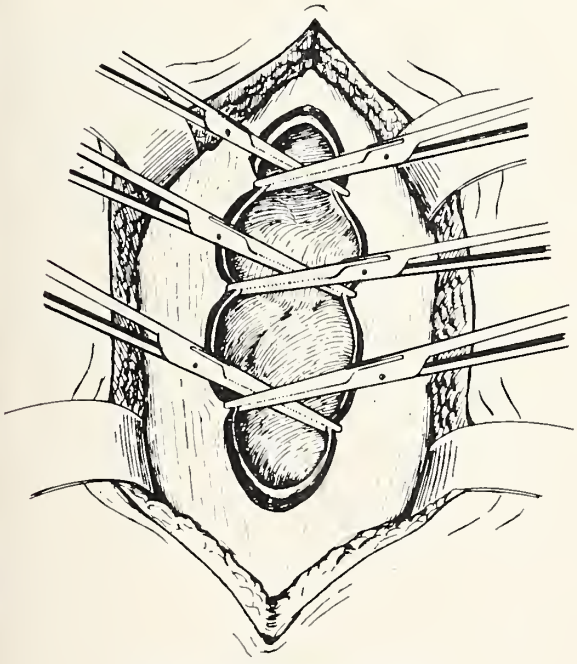


Figure 2.—Delineation of defect.

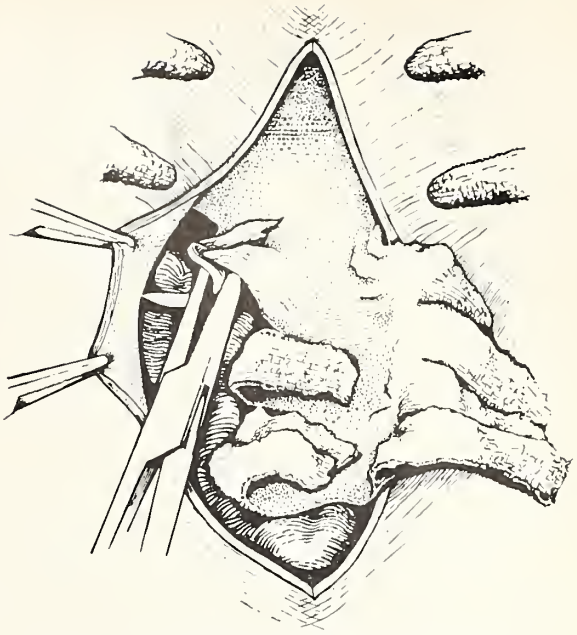


Figure 3.—Insertion of Marlex mesh prosthesis.

of the abdominal wall following the excision of a tumor. In one of the patients with hernia the defect occurred after a subcostal incision, in the other six after vertical incisions. One of the six had had a previous repair in which Marlex mesh was used as an onlay prosthesis but herniation recurred less than a year later.

The first of the seven patients was operated upon in February of 1965 and the most recent in September of 1966. All repairs were still intact as of December 1966. However, further follow-up will be required to evaluate this operation. Brief case histories follow.

Case 1.—A 42-year-old man had a defect 13 cm wide and 17 cm long in a right paramedian incision that had been made for a colon resection for carcinoma in March 1964. Repair was performed in February of 1965.

Case 2.—A 50-year-old woman had a hernial defect 12 cm wide and 15 cm long at the site of a paramedian incision for cholecystectomy done 12 years before. Repair was performed in October 1965.

Case 3.—A 64-year-old man had cholecystectomy in March of 1965. Dehiscence of the subcostal incision occurred on the fifth postoperative day, requiring repair. Herniation at the incision site developed in subsequent months. The defect

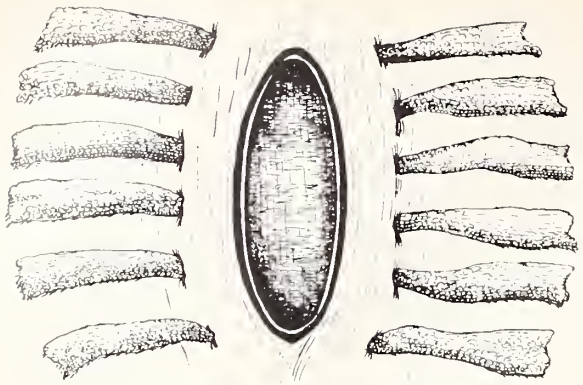


Figure 4.—Marlex mesh prosthesis in place.

was 12 cm by 18 cm. Repair was performed in November of 1965.

Case 4.—A 65-year-old woman had colon resection for carcinoma through a right upper paramedian incision in 1963. Recurrence developed two and a half years later, necessitating removal of a portion of the abdominal wall. A defect approximately 7 cm in diameter resulted. It was closed by use of the described technique in February of 1966. The closure remained intact until death in October of 1966.

Case 5.—A 51-year-old woman was operated upon in 1952 through a lower midline incision. The nature of the operation was not known. However a hernia followed several years later. The defect was 12 cm in width and extended from the umbilicus to the symphysis. Repair was performed in July 1966.

Case 6.—A 64-year-old woman had a hernial defect 8 cm wide and 12 cm long in a lower abdominal midline incision that had been made for a pelvic operation in 1954. Her hernia was repaired in August of 1966.

Case 7.—A 78-year-old clinic patient underwent cholecystectomy in 1963 and hernia developed at the site of the right paramedian incision. Repair of the hernia was carried out in November

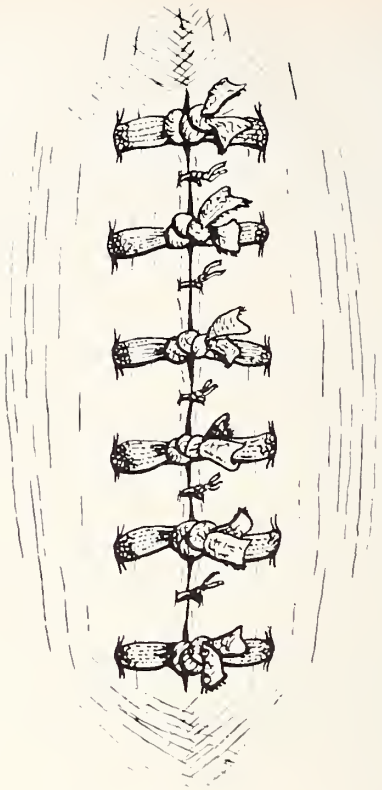


Figure 5.—Completed repair.

of 1964 by using Marlex mesh as an onlay support. In July of 1965, hernia recurred. The defect measured 10 x 20 cm. Reoperation, using the method described, was performed in August of 1966.

Case 8.—An 80-year-old woman had cholecystectomy through a paramedian incision in 1962. Postoperative infection occurred and a hernia followed. It was repaired in 1963 but recurred in the following months. The hernial defect was 10 x 15 cm when repair by the method here described was performed in September of 1966.

REFERENCES

1. Burton, C. C.: Fascia lata, cutis, and tantalum grafts in repair of massive abdominal incisional hernias, Surg. Gyn. Obst., 109:621-628, Nov. 1959.

2. Gallie, W. E.: Closing very large hernial openings, Ann. Surg., 96:551-554, Oct. 1932.

Pain in the Neck and Arm

Diagnosis by History and Examination

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■ *The cause of pain in the neck or pain in the arm coming from the neck can be accurately diagnosed by proper clinical examination. This requires knowledge of normal functional anatomy and understanding where pain can originate and what factors initiate the pain. The examination consists of testing for these abnormalities of motion and reproducing the symptoms by these motions.*

Weighing the history, both of trauma and indications of deep-seated tension or anxiety, against the conditions observed on physical examination, is important to correct diagnosis.

Recognizing abnormal neck posture and activities reprodncing pain in the neck and arm examination reveals the mechanism of pain. Treatment becomes evident.

A BASIC KNOWLEDGE of functional anatomy is required for the proper diagnosis and treatment of pain in the neck or in the arm originating in the neck. The examination must recognize the faulty function and the symptoms must be correlated with this abnormality. If the characteristic pain can be reproduced by a position or a movement and the exact nature of that position or movement is understood, the mechanism of pain production can then be appreciated.[1]

The cervical spine is an aggregate of superimposed functional units, with all units from the second cervical vertebra down to the first thoracic being similar one to another. A functional unit consists of two vertebral bodies separated by an intervertebral disk. This is the anterior weight-bearing part. The disks are wider anteriorly than posteriorly and are responsible for the lordotic shape of the cervical spine.[4] The disks are compressible and permit flexion, extension, lateral flexion and rotation of the neck.

The posterior portion of the functional unit consists of the pedicles, lamina, the transverse and posterior processes and the posterior articulations. These articulations are not primarily weight-bearing but act in a gliding manner to direct and limit the extent of neck motion.

The intervertebral foramen is bounded anteriorly by the posterior border of the disk annulus, the posterior longitudinal ligament, and the uncovertebral joints of von Luschka. The superior and inferior margins of the foramen are formed by the pedicles, and the posterior margin by the posterior articulations (facets). Through this foramen passes the spinal root (Figure 1). As the nerve root together with its sleeve of dura and arachnoid enters and passes through the intervertebral foramen, it is accompanied by small blood vessels and sympathetic nerves. The nerve root and its dural sleeve

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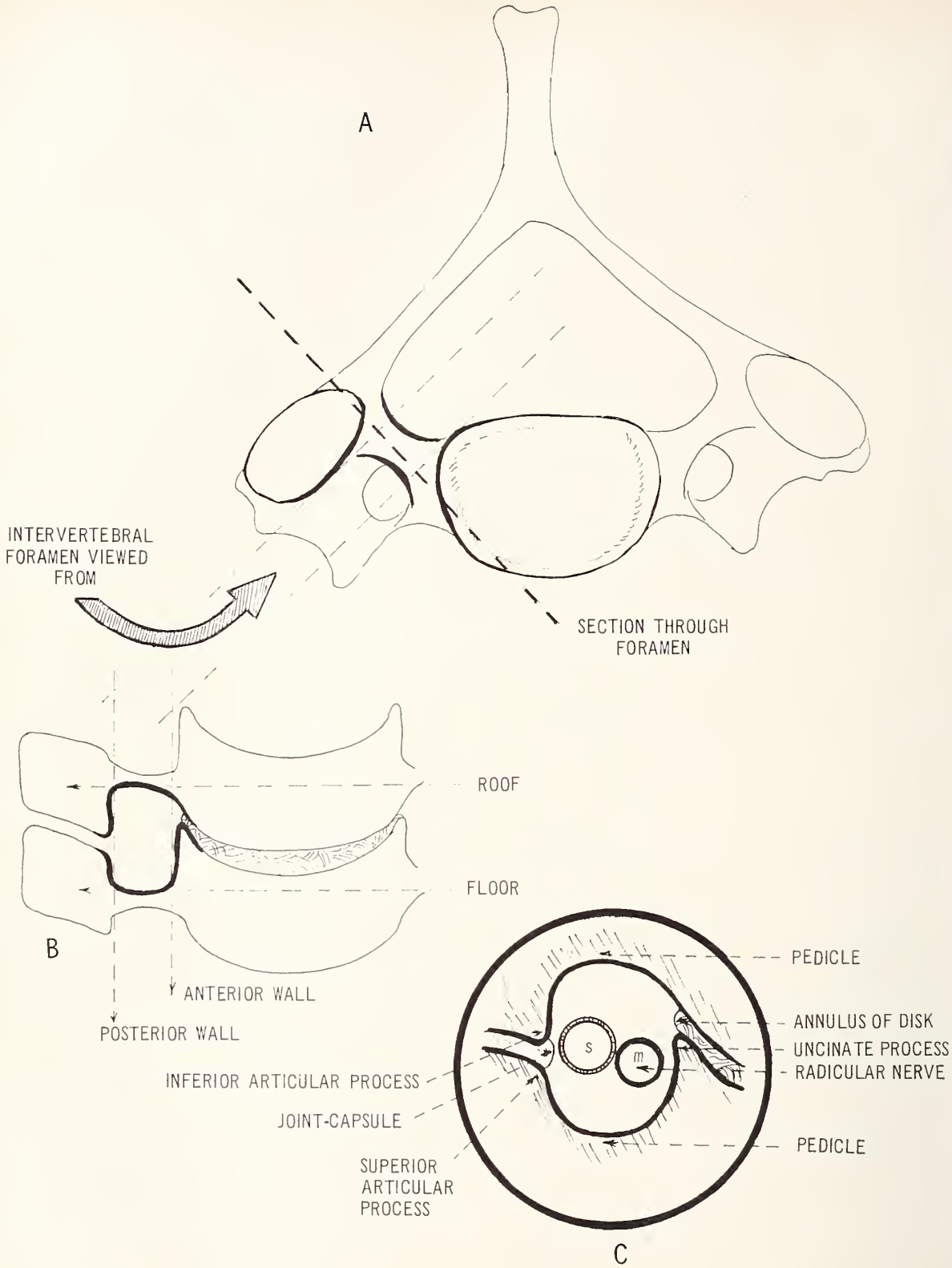


Figure 1.—Anatomical boundaries of the intervertebral foramen. As viewed from outside (arrow in A) the boundaries are shown in B. The relationship of the sensory (s) and motor (m) root components to the foramen are shown in C.

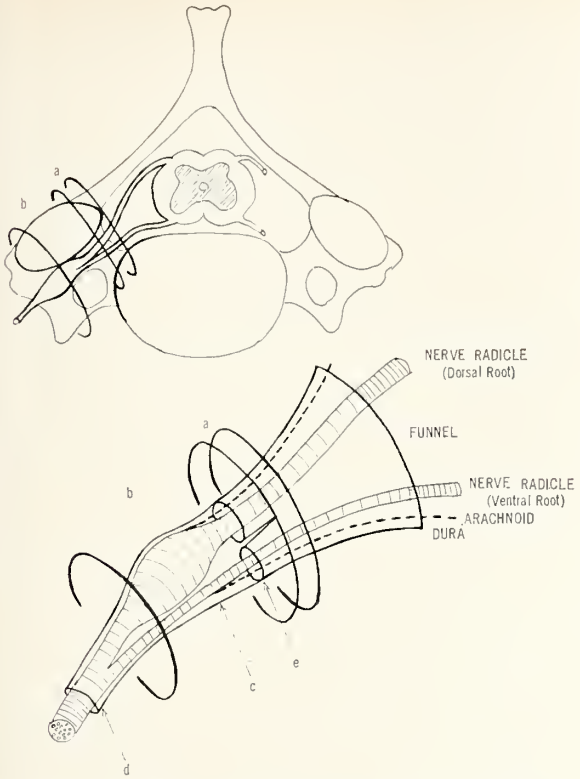


Figure 2.—The root "sleeve" in the intervertebral canal: A is the intervertebral foramen, B the gutter of the transverse process, C the termination of the attachment of the arachnoid.

(Figure 2) fill nearly half of the foramen and thus the root is susceptible to compression and inflammation if there is any impingement upon or narrowing of the foramen.[3]

Movement of the cervical spine below the second cervical vertebra is that of gliding, in which the second glides upon the third, the third upon the fourth, and so on.[8] As the spine flexes forward, the posterior facets separate and the foramina open (Figure 3). As the neck extends the foramina narrow. Rotation of the neck closes the foramen on the side toward which the head turns and opens them on the other side. External rotation and lateral flexion, as well as extension, are motions which may compress the nerve root where it passes through its foramen.

The spinal nerves are formed by numerous fila that merge into the roots which become enclosed in a dural sleeve.[3] The nerve emerges in the interspace above its similarly numbered vertebra with the exception of the eighth cervical which emerges above first thoracic. Each nerve has a specific motor and sensory function in the head, neck and upper extremity.



Figure 3.—"Gliding" motion of the cervical vertebrae. Motion of the third cervical through the seventh vertebra occurs by forward gliding in flexion and backward gliding on extension. Flexion (B) opens the intervertebral foramen.

The first two vertebrae are not structurally or functionally similar to the other functional units of the neck. There is no disk and no posterior facets between the occiput and the first cervical vertebra (atlas) nor between the first and second (axis). Therefore, the nerves that emerge at these levels do not pass through intervertebral foramina. They also do not innervate any sensory or motor component of the upper extremity. Their function is mostly sensory to the scalp and face. They are often involved in headaches which are caused by cervical tension in which they are irritated by muscular entrapment rather than by foraminal entrapment.

The movement of the occiput upon the atlas is one of slight flexion and extension as in a "nodding" motion of approximately 30°. No rotation or lateral flexion occurs at this joint. Motion between the atlas and the axis is one of rotation of 45° to either side and slight flexion-extension. In the absence of motion below the second cervical vertebra, the head is able to flex and extend 45° and to rotate 90°. This amount of motion remains in the severly fused neck of Marie-Strümpell spondylitis. The composite of motion possible in the cervical spine is illustrated in Figure 4.

Pain felt in the neck and in the arm originating in the neck has been attributed to arthritis and trauma. This may be a true assumption but it is more correct to attribute the cause of pain to encroachment on space and impairment of movement.

The tissues within the functional unit that are pain-sensitive are the posterior longitudinal ligament, the nerve root and its dural sleeve, and the posterior articular facets. All of these are in the region of the intervertebral foramen. The mechanism of pain production must therefore reside in abnormalities occurring here.

Disk herniation will encroach upon the posterior

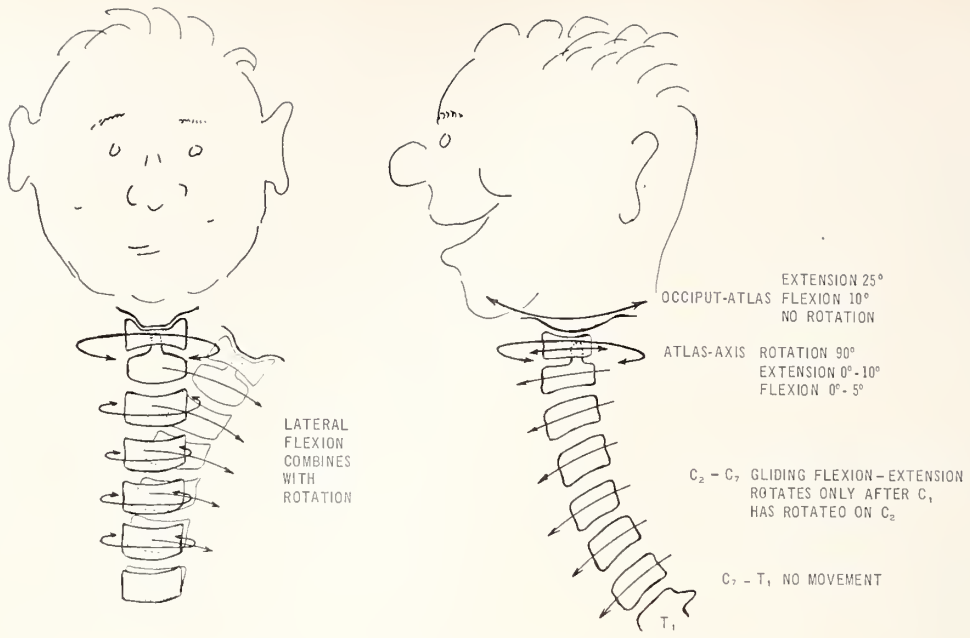


Figure 4.—Composite movements of the cervical spine.

longitudinal ligament or the nerve root and its sleeve, or on both. Degenerative disk disease will narrow the intervertebral space and thus decrease the foraminal opening.[6,11] Cervical spondylosis, so-called degenerative arthritis, encroaches on the foramen. Trauma may overstretch the supporting ligaments and cause excessive mobility and thus cause irritation of its enclosed tissues. Hyperextension of the neck from bad posture or from a position necessary in one's occupation may cause weight-bearing on the posterior articulations, which which in turn may cause synovitis or degenerative changes in the facets. History and examination of the patient will reveal the offending factors.

History and Examination

The history will elicit the activities or trauma or postures which initiated the pain and which will reproduce it.[7] The examination consists of determining the restriction of motion, the evaluation of the nerve roots involved and the reproduction of the painful symptoms by passive movement and positioning of the head and neck.

The examination begins with a viewing of the patient's posture. A "rounded" shoulder posture, excessive dorsal kyphosis or a "forward head" posture will cause an increase in the cervical lordosis. This attitude of the neck will approximate the posterior facets which may cause pain or may narrow the foramen and cause nerve root impingement. If this foraminal closure is repeated and aggravated by physical or emotional tension, the nerve roots and their sleeves become inflamed and swollen and they then occupy a greater portion of the already narrowed foramen. The nerve becomes edematous and engorged and pain occurs both in the neck and its place of referral, usually around the shoulder. Paresthesia and hypasthesia may be felt in the hand and arm.

The "tense person" — tense from emotional causes or physical postural fatigue — will have the erector spinae muscles in a state of sustained hypertonus. The muscles become painful and tender, the myofascial attachment to the occiput becomes painful and the entrapped greater superior occipital nerve becomes inflamed. Occipital vertex headaches supplement the cervical tension symptoms. Examination of patients of this kind will reveal the signs of deep-seated tension or anxiety. The neck does not move freely in any direction, and diffuse tenderness of all the neck muscles is palpable.

In post-traumatic sprain, as elicited by the history, the same "guarding" of neck motion will be noted. The spasm of the neck muscles will alter the curve of the cervical spine and will be seen roentgenographically as a "straightening." Initially, it is difficult to differentiate from the "tension" state, except for the history of trauma. When the patient is seen soon after the traumatic incident, especially

when the stress involved caused hyperextension of the neck, a reflex weakness of the neck flexors may be noted, with the patient unable to lift his head from the bed or examining table.[9] Ultimately in the post-traumatic sprain the limitation of motion persists only in extension and flexion, whereas in the emotional cervical "tension" state, motion in any direction is limited.

Pain may be referred from the neck into the shoulder area and the upper extremities. It consists of interscapular pain or of paresthesia into the arm, hand and fingers. As the encroachment on the nerve occurs in the foramen, specific neck movements should reproduce the symptoms. Neck extension and rotation of the neck toward the involved side will close the foramen there. This motion thus compresses the entrapped nerve and should reproduce the symptoms in the arm, hand and fingers. If a protrusion of an intervertebral disk is suspected, flexion may cause an aggravation of the symptoms by placing traction upon the nerve.

The cutaneous area supplied by a single nerve root is known as a dermatome. The pain or paresthesia claimed by the patient is referred to the specific dermatome.[5] The group of muscles supplied by a single nerve root is known as a myotome. The clinical examination of the upper extremity by evoking deep tendon reflex and by muscle testing reveals the specific nerve root and differentiates the lesion as a root envolvement rather than a peripheral nerve lesion.[6]

The most frequently involved nerve roots are the sixth, seventh and eighth cervicals since the greatest motion and greatest degree of disk degeneration occurs between the fifth and sixth and the sixth and seventh. Encroachment upon the sixth cervical nerve root will cause paresthesia and hypasthesia of the thumb and index finger, weakness of the biceps muscle and reduction of the biceps jerk. Pain may be referred to the interscapular and shoulder area. Pressure on the seventh cervical nerve root will cause sensory changes of the index and middle finger, weakness of the triceps and depression of the triceps tendon reflex. Similar encroachment on the eighth nerve will bring about sensory changes in the little finger but there will be no reflex changes and whatever muscular weakness there is will be in the small muscles of the hand.

Clinical examination based on concepts of functional anatomy can reveal the pathological mechanism by which pain is caused. Roentgenograms, studies with contrast medium (Pantopaque®) and other tests such as electromyography can merely confirm the clinical impression.

Treatment

Treatment based on functional anatomical and physiological concepts can be directed toward alleviating the offending mechanisms.[10] Immobilization to permit abatement of ligamentous strain, muscle spasm or nerve root entrapment must place the neck in slight flexion. This position separates the posterior facets and opens the foramen. Posture training in daily living and in occupational situations must keep this concept in mind. Traction, to be effective, must also flex the spine rather than attempt merely to distract the vertebrae.[2] Exercise must have a specific intent. Active motion when the entrapped nerve is edematous and fills the greater portion of the foramen must be avoided. Ultimately exercise must increase range of motion but it must always be done with the neck in the slightly flexed neutral position.

Whatever pathologic changes may have taken place in the cervical spine as a result of degenerative changes called "arthritis," will remain. The symptoms caused by trauma, whether from sudden injury, from bad posture or from emotional stress to the neck, can be relieved.

Figures are reproduced from: Neck and Arm Pain, R. Cailliet, F. A. Davis Company, Philadelphia 1964.

REFERENCES

1. Cailliet, R.: Neck and Arm Pain, F. A. Davis Company, Philadelphia, 1964.
2. Colachis, S. C., and Strohm, B. R.: A study of tractive forces and angle of pull on vertebral interspaces in the cervical spine, Arch. Phys. Med. and Rehab., 46:820-830, Dec. 1965.
3. Frykholm, R.: Cervical Nerve Root Compression Resulting from Disc Degeneration and Root Sleeve Fibrosis; A Clinical Investigation, Acta Chir. Scandinav., Supp. 160, 1951.
4. Hadley, L. A.: The Spine: Anatomica-Radiographic Studies, Development and the Cervical Region, Charles C Thomas, Springfield, Ill., 1956.
5. Haymaker, W., and Woodhall, B.: Peripheral Nerve Injuries, 2nd Ed., W. B. Saunders Co., Philadelphia, 1953.
6. Holt, S., and Yates, P. O.: Cervical spondylosis and nerve root lesions, J. Bone and Joint Surg., 48-B: No. 3, 407-423, Aug. 1966.
7. Jackson, R.: Cervical Syndrome, Charles C Thomas, Springfield, Ill., 1958.
8. Jones, M. D.: Cineradiographic studies of the normal cervical spine, Cal. Med., 93:293-296, Nov. 1960.
9. Krout, R. M., and Anderson, T. P.: Role of anterior cervical muscles in production of neck pain, Arch. Phys. Med. and Rehab., 47:603-611, Sept. 1966.
10. Rubin, D.: Head, neck, and arm symptoms subsequent to neck injuries; physical therapeutic considerations, Arch. Phys. Med. and Rehab., 40:387-389, Sept. 1959.
11. Teng, P.: Spondylosis of the cervical spine with compression of the spinal cord and nerve roots, J. Bone and Joint Surg., 42-A:392-407, Apr. 1960.

Cytologic Diagnosis of Gastric Cancer

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■ *Follow-up of cytologic examinations of specimens obtained from 187 patients by gastric lavage with saline solution, without the use of enzymes or abrasive devices, showed a false positive rate of 0.6 per cent and a false negative rate of 17 per cent.*

To achieve satisfactory results with such examinations, great attention to detail in obtaining, preparing and examining the specimens is essential. Cytologic examination should be done in any case in which gastric cancer is suspected clinically or roentgenographic or gastroscopic findings arouse suspicion.

EXFOLIATIVE CYTOLOGY is very useful in the diagnosis of carcinoma of the stomach. The clinical diagnosis of early gastric carcinoma is notoriously inaccurate. Radiologic study of the stomach, although 90 to 95 per cent accurate in detecting the presence of a gastric lesion, is only 70 to 80 per cent accurate in distinguishing whether the lesion is benign or malignant.[3,5,8,12] It is even less accurate in the detection of superficial spreading carcinoma of the stomach. Gastroscopy has comparable limitations in accuracy, besides being uncomfortable for the patient and technically difficult.[3,5] Exfoliative cytology has been shown by several investigators[3,5,11] to be more accurate than roentgenography or gastroscopy in determining whether a gastric lesion is malignant, and it is simple enough to be performed in any pathology laboratory that has well trained cytotechnologists.

The cytologic diagnosis of gastric carcinoma was first reported by Beale[1] in 1858 after he had examined unstained smears of vomitus for malignant cells. Marini[7], who in 1909 was the first to use gastric lavage for obtaining the specimens, detected malignant cells on unstained smears of aspirate in 32 of 37 cases of gastric carcinoma. The first report of the staining of smears of gastric aspirate for cytologic examination was made by Loeper and Binet[4] in 1911. After a 30-year hiatus, a great resurgence of interest followed the work of Papanicolaou who in the 1940s extended his studies on gynecologic exfoliative cytology to the stomach and other anatomic sites.[10] During the past decade, several series have been recorded which demonstrate the accuracy of the procedure (see Table 1).

Present Series

Gastric lavage with saline solution to obtain specimens for cytologic examination (a technique previously described by other investigators[9,10,11]) has been used for more than six years at the Hospital of the Good Samaritan Medical Center, Los Angeles. It has proved most useful in determining whether cancer is or is not present in suspected cases. The technique is relatively simple, and the accuracy of results is comparable with that achieved when more complex aspiration procedures are used to obtain gastric cells for cytologic

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TABLE 1.—*Review of Literature Relative to Accuracy of Exfoliative Gastric Cytology in Diagnosis of Cancer*

Date	Reported by (Reference)	Total Number of Cases	False Negatives (Proved Gastric Cancer)			False Positives (Proved or Apparently Benign)		
			Cases	False	Per Cent False	Cases	False	Per Cent False
1960	Schade (9)	558	282	6	2	276	13	5.0
1962	Von Haam (13)	1,050	50	7	14	1,000	14	1.4
1963	MacDonald (5)	380	89	6	7	291	1	0.3
1964	Yamada (14)	337	181	34	19	156	5	3.0
1964	Henning (3)	380	227	39	17	153	6	4.0
1965	Taebel (11)	1,866	282	53	19	1,584	4	0.25
1967	Present report	184	29	5	17	155	1	0.6

study. In one of the more elaborate methods, the proteolytic enzyme chymotrypsin, which is said to increase the yield of exfoliated cells by dissolving the coat of mucus over the gastric mucosa, is added to the lavage solution.[5,6,14] Other investigators advocate the use of various abrasive devices or sponges[3] to cause exfoliation of mucosal cells. These techniques are not only more complex but they cause the patient discomfort and they entail some risk. We have found the saline lavage to be simple, free of discomfort and complications, and productive of well preserved exfoliated cells in adequate number.

Technique

The entire aspiration procedure is performed by cytotechnologists or nurses trained and supervised by physicians in the Department of Pathology. (Random specimens obtained by untrained nurses or other untrained personnel are generally useless, for usually they contain few exfoliated cells and even those present are badly degenerated.)

The evening before the specimen is to be obtained, the patient is permitted to have only a light liquid meal. To assure adequate hydration, he must drink several glasses of water at bedtime and on arising. He cannot have breakfast. A No. 18 rubber Levin tube, not lubricated, is passed through the mouth into the stomach to the 55 or 60 cm mark. The gastric residual fluid is then aspirated, checked for free acid, and discarded. A 50 ml catheter irrigation syringe with a large orifice is used to wash the stomach twice with 300 to 500 ml of normal saline solution. Each time the solution is repeatedly and vigorously injected, aspirated, reinjected and reaspirated. The first lavage serves to remove the mucous coat and the aspirated liquid is discarded; the material aspirated after the second lavage is saved for cytologic examination. During lavage the patient changes position, from prone to supine to one side and then the other, and the abdomen is massaged while he is supine. Also, the position of the tube is moved frequently to assure irrigation of large areas of gastric mucosa.

The aspirate from the second lavage is immediately placed in glass specimen bottles which are already immersed in ice. The specimens are kept in ice and are immediately returned to the laboratory for processing. Speed is essential and is the key to accurate interpretation, since gastric enzymes and acid rapidly destroy the cells. The aspirate is centrifuged on a table top centrifuge at high speed for 5 minutes in 40 ml cylindrical glass centrifuge tubes. The supernatant is decanted and a spatula is used to smear the sediment on clear glass slides previously coated with a thin layer of albumin. Four slides are prepared for each case. The slides are fixed in Carnoy's medium* for a half hour to two days. This causes lysis of any erythrocytes that may be present. The smears are stained with regular Papanicolaou stain and are screened by trained cytotechnologists. Final interpretation is made by a pathologist. It should be

*Carnoy's medium is prepared by mixing 70 ml of 95 per cent ethanol, 25 ml of chloroform, and 5 ml of glacial acetic acid.

TABLE 2.—*Follow-up of Gastric Cytologic Examinations*

Cytologic Diagnosis		Total Number of Cases	Proved or Apparently Benign	Proved Malignant	No Follow-up
Negative—	Class I—Normal and Class II—Atypical	158	153	5	0
Suspicious—	Class III	5	1	2	2
Positive—	Class IV—Very Suspicious and Class V—Malignant	24	1	22	1

TABLE 3.—*Accuracy of Gastric Cytologic Examination*

Final Diagnosis	*Total Number of Cases*	*False Negative*	*False Positive*
Proved or Apparently Benign	155	...	1 of 155 (0.6%)
Proved Malignant	29	5 of 29 (17%)	...

noted that if both cytologic examination and timed gastric analysis for acid are desired, the lavage for cytologic specimens is performed first.

Results

In a period of five and a half years between January 1961 and June 1966, 187 inpatients at The Hospital of the Good Samaritan Medical Center had gastric cytologic examinations. Follow-up was obtained on 184. Of 155 patients who ultimately were proved not to have gastric cancer only one had a cytologic test interpreted as positive, a false positive rate of 0.6 per cent. In that one case the interpretation was Papanicolaou Class IV (very suspicious of cancer). In none of the cases in which the interpretation was Class V (diagnostic for malignant disease) did the patient prove not to have cancer. Of the 29 cases in which malignant disease was later proved, five were missed cytologically, the slides being interpreted as Class I or Class II. Thus the false negative rate was 17 per cent. Four of the 29 patients with malignant disease had malignant lymphomas and the remaining 25 had adenocarcinomas. Of the 24 cases with positive cytologic diagnosis (Class IV and Class V), ten were of Class IV and 14 Class V. Of the 24 patients with diagnosis of "positive" by cytologic examination, 22 proved to have cancer, one was proved not to have the disease and adequate follow-up was not available on the remaining case. In only five of the 187 cases was the slide read as Class III (suspicious); we attempt to hold the number of Class III reports to a minimum as this classification is least helpful to the clinician.

There are situations in which cytologic examination of material obtained by gastric lavage are of particular value, as in the following cases:

CASE 1.—A 61-year-old white woman was well until the sudden onset of gastrointestinal bleeding. X-ray studies showed a 2.5 cm ulcerated lesion on the lesser curvature of the stomach. The radiologist was unable to determine whether it was benign or malignant. Gastric cytologic examination was positive (Class V), with cells characteristic of adenocarcinoma (Figures 1 and 2). Radical total gastrectomy was performed. The lesion was an

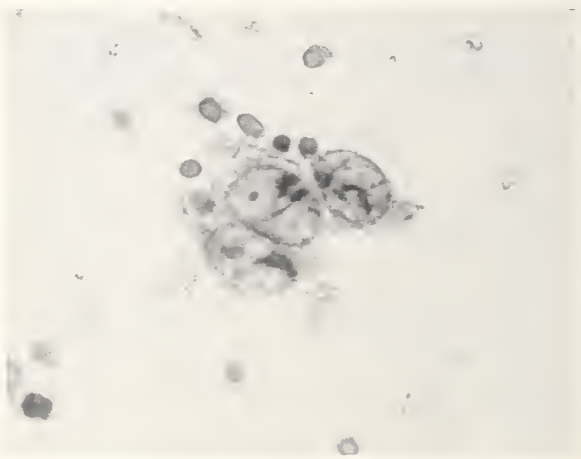


Figure 1.—(Case 1) Adenocarcinoma ×1,000.

ulcerating adenocarcinoma with metastasis to lymph nodes along the lesser curvature.

Comment: The ulcerated gastric lesion was detected radiologically but, as frequently happens, a decision could not be made as to whether it was a benign peptic ulcer or an ulcerated adenocarcinoma. A definitive diagnosis of malignant disease was made cytologically. Having a definitive diagnosis, the surgeon was able to proceed directly with a radical total gastrectomy without the necessity of first opening the stomach and taking a specimen of the lesion for frozen section.

CASE 2.—A 63-year-old white woman first had had gastric ulcer on the lesser curvature, diagnosed

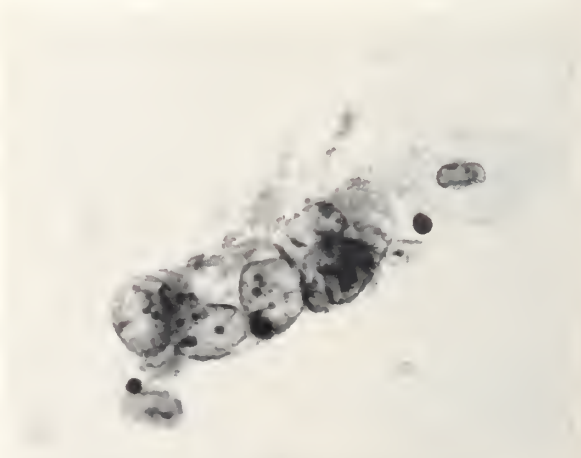


Figure 2.—(Case 1) Adenocarcinoma ×1,000.

radiologically, in 1957. It completely healed on conservative therapy. In 1961, after recurrence of epigastric pain, x-ray studies were normal and gastroscopy was unsuccessful; gastric cytologic study then was negative (Class II). Conservative therapy was again successful until early in 1963, when symptoms recurred. X-ray studies revealed redundant mucosa high on the lesser curvature, and gastric cytologic smears were again interpreted as Class II, with atypical cells present but no malignant cells identified. In March 1963, at gastrotomy, a large circumferential juxta-esophageal gastric ulcer was found. Biopsy of the lesion showed only atypical epithelial hyperplasia, and distal gastrectomy and vagotomy were performed. X-ray studies later showed healing of the ulcer, but dysphagia persisted. In December of 1963, repeat cytologic examination showed malignant cells characteristic of adenocarcinoma (Class V). Surgical resection of the proximal stomach was then done and it contained a superficial spreading carcinoma arising in the margins of a chronic peptic ulcer of the cardia. There was a single minute metastatic focus in one gastric lymph node. Laparotomy in November 1965 to relieve intestinal obstruction showed peritoneal carcinomatosis, proved by biopsy. The patient died in May 1966.

Comment: The long history of benign gastric ulcer, documented by x-ray studies and biopsy, was followed six years later by the development of a superficial spreading adenocarcinoma of the stomach, which was detected only by positive gastric cytologic examination. Schade[9] described 16 cases of superficial spreading or surface carcinoma, and he expressed belief that in all such cases there is accompanying chronic gastritis. Carcinoma of this type may sometimes be diagnosed cytologically in an early curable stage, before it is radiologically or gastroscopically detectable. Unfortunately in this case metastasis had already occurred.

Case 3.—A 75-year-old white man had a two-month history of epigastric pain. X-ray films revealed a defect on the greater curvature. felt to be an early carcinoma. Gastric cytologic examination (Figure 3) revealed cells very suspicious for malignant change (Class IV). At operation a mass was found along the greater curvature with grossly enlarged lymph nodes. Biopsy showed a reticulum-cell sarcoma. Despite radiation therapy, the patient died about a year later.

Comment: Not only adenocarcinoma but also

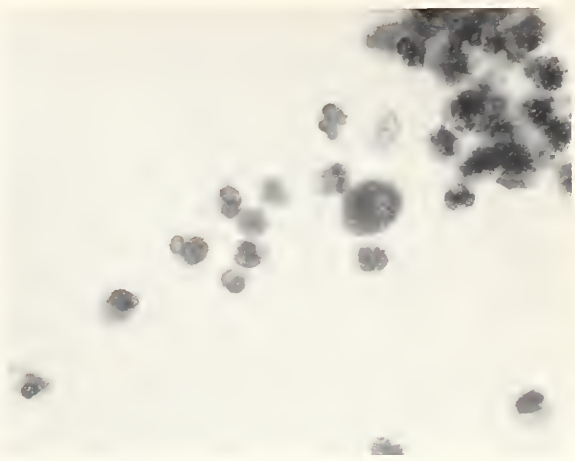


Figure 3.—(Case 3) Reticulum-cell sarcoma ×1,000.

malignant lymphoma of the stomach may be detected cytologically. The differentiation of adenocarcinoma and reticulum-cell sarcoma by cytologic examination of gastric aspirates is difficult. Although the malignant cells in this case were detected cytologically, they were not specifically identified as being from a reticulum-cell sarcoma. (Three other cases of malignant lymphoma were included in the present series, and in two of them the cytologic smear was called positive and the lesion identified as lymphoma. One case was not diagnosed cytologically, and hence is included among the false negative cases.)

Discussion

The degree of accuracy attained in this series, and that reported by other investigators provides reasonable assurance that if the result of a properly executed gastric cytologic examination is negative. gastric malignant disease is unlikely. Obviously. in all reported series some false negatives occur, and gastric cytology should not be the sole technique used to exclude the diagnosis of gastric cancer. An unequivocal positive report (Class V), however, is highly significant and should be considered as a definitive diagnosis of cancer.

In order to achieve satisfactory results, attention to detail is essential. The specimen should be obtained only by specially trained cytotechnologists or nurses. Random gastric aspirations obtained by untrained personnel and sent routinely to the laboratory are usually unsatisfactory. Speed in the preparation and fixation of the smears, with immediate chilling of the aspirate, is absolutely essential to prevent cellular degeneration.

The criteria used in identifying malignant cells are essentially the same as those applicable in other anatomic sites such as the female genital tract and respiratory system. These criteria include enlarged nuclei with increased nucleocytoplasmic ratio, variation in nuclear size, irregular chromatin clumping, hyperchromasia of nuclei, and enlarged and multiple nucleoli. It must be emphasized that hyperplastic epithelial cells from the margins of a benign ulcer and from cases of chronic gastritis or pernicious anemia can mimic some of the criteria of malignancy, and the pathologist who interprets the smears should be trained and experienced in this field of exfoliative cytology. If a pathologist interested and trained in this area of cytopathology is available, results comparable with those reported from large centers may be achieved in smaller hospitals with a relatively small number of cases.

Since gastric exfoliative cytology, unlike vaginal cytology, is time-consuming and expensive, it is not suitable as a routine screening procedure for all patients in the cancer age group. However, it should be done in any case in which a patient of "cancer age" has gastrointestinal symptoms suggestive of gastric cancer, or has any significant gastric abnormality on x-ray or gastroscopic examination or any other abnormalities arousing suspicion of cancer. It is also useful in the post-gastrectomy follow-up of patients with known gastric cancer, since recurrences are often easily detected.[11] Finally, it may be worth while to carry out periodic screening of certain specific groups at high risk of gastric carcinoma, such as patients with pernicious anemia[2,6] (we have had no specific experience with this latter category of patients).

REFERENCES

1. Beale, L. S.: The microscope in medicine, 2nd ed., 1858, J. and A. Churchill, LTD.

2. Boon, T. H., Schade, R. O. K., Middleton, G. D., and Reece, M. F.: An attempt at presymptomatic diagnosis of gastric carcinoma in pernicious anemia, Gut, 5:269-270, 1964.

3. Henning, N., Witte, S., and Bressel, D.: The cytologic diagnosis of tumors of the upper gastrointestinal tract (esophagus, stomach, duodenum), Acta Cytologica, 8:121-130, 1964.

4. Loeper, M. and Binet, E.: Le cytodiagnostic des affections de l'estomac, Bull. Soc. Med. Hop. (Paris), 31: 563, 1911.

5. MacDonald, W. C., Brandborg, L. L., Taniguchi, L., and Rubin, C. E.: Gastric exfoliative cytology: An accurate and practical diagnostic procedure, Lancet, 2:83-86, 1963.

6. MacDonald, W. C., Brandborg, L. L., Taniguchi, L., Beh, J. E., and Rubin, C. E.: Exfoliative cytological screening for gastric cancer, Cancer, 17:163-169, 1964.

7. Marini, G.: Uber die diagnose des magencarcinomas auf grund der cytologischen untersuchung des Spülwassers, Arch. Verdauungskrankh, 15:251, 1909.

8. Schade, R. O. K.: A critical review of gastric cytology, Acta Cytologica, 3:7-14, 1959.

9. Schade, R. O. K.: Gastric cytology: Principles, methods, and results, 1960, Edward Arnold (Publishers), LTD., London.

10. Seybolt, J. F., Papanicolaou, G. N. and Cooper, W. A.: Cytology in the diagnosis of gastric cancer, Cancer, 4:286-295, 1951.

11. Taebel, D., Prolla, J., and Kirsner, J.: Exfoliative cytology in the diagnosis of stomach cancer, Annals Int. Med. 63:1018-1026, 1965.

12. Taebel, D., and Kirsner, J.: Exfoliative cytology of the upper gastrointestinal tract, JAMA, 199:570-573, 1967.

13. Von Haam, E.: A comparative study of the accuracy of cancer cell detection by cytological methods, Acta Cytologica, 6:508-518, 1962.

14. Yamada, T., Matsumoto, S., Sankawa, H., and Seino, Y.: Clinical evaluation of proteolytic enzyme lavage method in gastric cytodiagnosis, especially in the detection of early cancer of the stomach, Acta Cytologica, 8:27-33, 1964.



Stretch Garment Dermatitis

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■ *A disease of the skin, not hitherto described, is caused by pressure or tension on the skin from the wearing of tight-fitting stretch garments such as "stretch bras," "stretch girdles" and "stretch socks." The condition is not due to chemical sensitization of fabrics, dyes or other additives but is of mechanical origin.*

The eruption may assume various clinical forms and may be characterized by a nondescript erythematous and eczematous appearance or may consist of an exaggeration, in the areas covered by the stretch garment, of already existing dermatosis such as lichen planus, psoriasis, acne vulgaris, discoid lupus erythematosus or atopic dermatitis.

IT IS WELL KNOWN that the elastic bands commonly present in both men's and women's underwear and nightclothes are frequently the cause of irritation to the skin. This is especially true if the elastic material is rubberized or is unusually tight-fitting. Often such skin irritations are the result of a true allergic contact sensitivity, confirmed by positive reactions to patch tests to material from the elastic bands.[2] Furthermore, allergic skin reactions, again confirmed by positive patch tests, have been elicited by the synthetic yarn Spandex® in brassieres, as reported by Allenby,[1] by Porter and Sommer,[5] and by Stewart, Danto and Maddin.[8] We have ourselves seen at least one instance of allergic sensitivity to the Lycra® panels which composed the expandable parts of both a stretch bra and a stretch girdle.

The skin eruptions with which we are concerned in this communication, however, are apparently not truly allergic in nature but are the result of friction and pressure applied to a localized area of skin for a fairly protracted length of time. Considering that Ribaudo and Formato,[6] and Craig and Dvorak,[3] under the appropriate title "Panty Girdle Syndrome," have described an obstructive vascular reaction to a commonly-used stretch garment, it is not surprising that an article of clothing capable of producing such relatively deep-seated injury should be capable of irritation to the overlying skin. Stretch garment dermatitis may well be merely a more severe and extensive form of the friction dermatitis caused by the elasticized bindings mentioned above. The fact that it *is* more extensive and can be more severe is, we think, justification for attempting to describe it and bring it to the attention of skin specialists. In addition, we are likely to be seeing more of it, since stretch garments have proved to be highly acceptable to the buying public. Furthermore, the textile industry seems bent on developing more and ever newer fabrics that lend themselves well to the design of stretch-type garments.

Of course, these articles of apparel are also subjected to the various dyes and additives intended to give them a lustrous surface, or to make them wrinkle-resistant and "drip-dry" as are clothes of the non-stretch variety. Such dyes and additives may produce adverse cutaneous reactions, but usu-

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ally on the basis of an allergic contact sensitization. These reactions were classically described by Schwartz and Peck[7] in 1945.

To conform to the criteria we have arbitrarily set up for stretch garment dermatitis, the skin outbreak should not be the result of sensitivity to a chemical but should be of mechanical origin — that is, it should be the result of friction or pressure caused by the wearing of a tight-fitting article of clothing made of an elasticized fabric. Such factors as movement of the skin surface under the garment with each bodily motion, and the tropical environment of the skin caused by increased heat and humidity resulting from the tight fit would be aggravating factors.

Stretch garment dermatitis assumes two principal clinical forms: (1) A nondescript, erythematous and eczematous eruption, usually nonexudative, confined to the area of the body covered by the stretch garment and perhaps most severe where the garment binds most closely; and (2) an exaggeration, in the areas covered by the stretch garment, of already existing dermatosis. The stretch garment dermatitis that first came to our notice was of the former variety, but it was the latter type that started us thinking of it as an entity.

Early in 1965 we became aware that some of our adolescent girl patients undergoing treatment for acne were showing relatively poor response to usually effective therapy on the shoulders and back, even though the acne on the face and chest was improving in a satisfactory manner. It soon became obvious that what these girls had in common, besides the lack of response noted, was the wearing of very tight-fitting stretch bras. Closer observation showed that the number of comedones, papules and papulopustules was much increased under the bra straps where they crossed the shoulders and traversed the scapulae, and also on the lower back under the cross-strap. Usually a slight increase in acne activity was also demonstrable in a zone about one-half to one centimeter on either side of the straps, corresponding to the zones of friction where the bra rubbed with arm movement. On one patient in particular, from the back view, acne activity showed almost a perfect outline of her brassiere. The breasts, not being an area of usual acne outbreak, showed no such picture. Friction from the upper border of the bra "cup" showed a tendency to aggravate acne on the adjacent areas of the chest, however, and acne on the anterior surface of the shoulders and the clavicular regions could be made worse by the elastic straps.

When we counseled this group of patients to resume the wearing of the old style nonelastic brassieres, the limited availability of these quaint memorabilia from the past became evident. Brassieres made of elasticized material are now so widely used that, we have been advised, the "ordi-



Figure 1.—Stretch garment acne. View of shoulder from above and rear, showing accentuation of papules, pustules and comedones where elastic strap rubs.

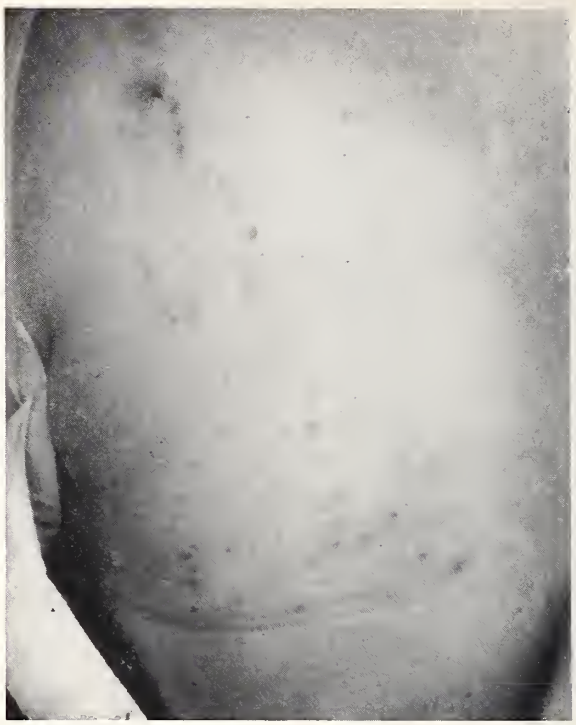


Figure 2.—View of back, same patient as Figure 1, showing increased concentration of papules and papulopustules where the arm straps cross the scapular area and where the cross strap traverses the midback.



Figure 3.—Nondescript eczematous dermatitis on the outer aspect of the left hip, corresponding to area of friction from stretch panel in patient's girdle.

nary" kind has become difficult to find. It seems that not many department or women's specialty stores carry them, and those that do prefer to keep them hidden in the far reaches of the stockrooms.

Among other specific dermatologic outbreaks we have seen aggravated by the wearing of stretch garments are pruritus hiemalis, lichen planus, chronic discoid lupus erythematosus (see figures) and atopic dermatitis.

Discussion

From the diversified morphologic features of the dermatitis described, it is evident that stretch garment dermatitis is not a morphological entity. What all the patients have in common is a skin eruption produced by the friction and close pressure of elasticized fabric, or else the aggravation of a pre-existing skin condition in those areas of the body in most intimate contact with such fabric. For this reason stretch garment dermatitis may be considered an entity from an etiologic if not from a morphologic or pathological standpoint. Since the causative factors we are considering here are essentially traumatic in nature, it could perhaps be argued that stretch garment dermatitis is merely



Figure 4.—Pruritus hiemalis, aggravated by friction from the stretch brassiere. Photograph of the center of the back.

a variation of the Koebner isomorphic phenomenon, as Farber and Carlsen pointed out in their paper on psoriasis in childhood.[4] This is perhaps true, but stretch garment dermatitis seems to occur just as readily in the instance of banal skin diseases as it does with the acute eruptive forms. Perhaps the name "stretch garment dermatitis" is not completely accurate, either. We have adopted it as a matter of convenience because most of the skin eruptions produced by the friction of closely fitting wearing apparel result from the use of clothes made from elasticized material. Recently, however, we have become increasingly aware of similar outbreaks caused by clothing not made of stretch material as such. The present fashion for

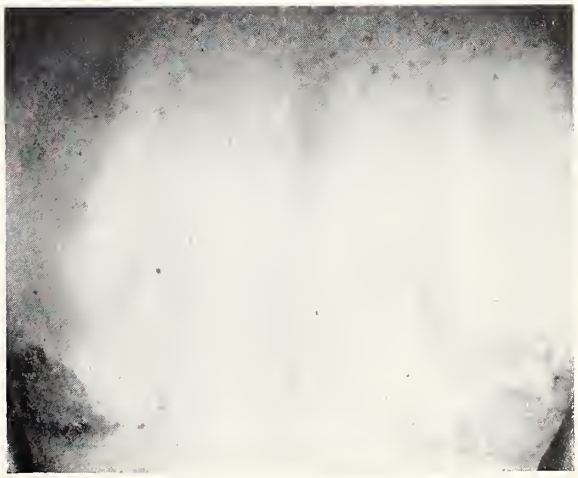


Figure 5.—Stretch garment dermatitis. Chronic discoid lupus erythematosus occurring symmetrically on posterolateral aspects of chest wall, where stretch bra binds. Smaller plaques of discoid lupus erythematosus were present under the arm straps.

short-rise trousers with extremely narrow cut to the legs, especially popular among adolescent and young adult males, has been responsible, we feel, for such problems as pruritic inflammatory and lichenified dermatitis of the scrotum, for folliculitis of the anterior surfaces of the thighs, and for aggravation of a pruritus hiemalis and atopic dermatitis of the thighs and legs. Although as dermatologists we may deplore the increased popularity of such potential cutaneous irritants, so long as they *are* in style and have advantages over the older types of fabrics in the viewpoint of the wearer and retailer, they are going to be worn and we are going to see more and more skin problems brought on by them.

REFERENCES

1. Allenby, C. F., Crow, K. D., Kirton, V., and Munro-Ashman, D.: (Correspondence) British Med. J., 1, 674, 12 Mar. 1966.

2. Bowyer, C. F., and Alexander, S.: Fashion in dermatology, Practitioner, 195:215-217, Aug. 1966.

3. Craig, A. B., Jr., and Dvorak, M.: Constrictive forces of panty girdle on thigh, N.Y. State J. of Med., 65: 1337-1338, 1 June 1965.

4. Farber, E. M., and Carlsen, R. A.: Psoriasis in childhood, Calif. Med., 105:416-419, Dec. 1966.

5. Porter, P. S., and Sommer, R. G.: Contact dermatitis due to Spandex, Arch. Derm., 95:43-44, Jan. 1967.

6. Ribaudo, C. A., and Formato, A. A.: Panty girdle syndrome, N.Y. State J. of Med., 65:456-457, 1 Feb. 1965.

7. Schwartz, C. F., and Peck, S. M.: Dermatitis from wearing apparel, JAMA, 128:1209-1217, 25 Aug. 1945.

8. Stewart, W. D., Danto, J. L., and Maddin, S.: Synopsis of dermatology, C. V. Mosby and Co., St. Louis, p. 102, 1966.



Epidemiology of Leptospirosis in California: A Cause of Aseptic Meningitis

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■ *Twenty-one cases of leptospirosis, including three that were fatal, were reported in California during 1961-1965. An additional 18 cases were detected for the same period by screening sera from patients with central nervous system (CNS) disease of suspected viral origin. This finding supports a hypothesis that leptospirosis frequently is not considered in the differential diagnosis of CNS disease in which viral infection is suspected.*

The 39 patients, six of them females, ranged in age from six to 66 years. Most infections occurred in the summer. A history of exposure to animals or of swimming in potentially contaminated waters was obtained from 32 of the 39.

INFECTIOUS JAUNDICE (Weil's disease) is the classic clinical syndrome caused by leptospires. The etiologic agent usually considered is *Leptospira icterohemorrhagiae*. Most leptospiral serotypes, such as *L. canicola* and *L. pomona*, rarely produce jaundice. Leptospires may cause aseptic meningitis that is difficult to distinguish from the syndrome initiated by a variety of viral agents.

This report discusses the epidemiologic findings on 39 cases of leptospirosis occurring in California during 1961-1965, including 18 cases detected in a survey of paired sera from 540 patients with central nervous system (CNS) disease of undetermined origin.

Submitted 30 June 1967.

Reprint requests to: National Communicable Disease Center, USPHS, Zoonoses Section, Ecological Investigations Program, 15th Avenue and Lake Street, Building 18, San Francisco 94118 (Dr. Hubbert).

Material and Methods

Data concerning reported cases were obtained from epidemiologic history forms returned to the Bureau of Communicable Diseases, California State Department of Public Health. The Viral and Rickettsial Disease Laboratory, California State Department of Public Health, provided paired sera from 540 patients with CNS disease of suspected viral origin submitted during 1961 and 1963-1965.

These 540 patients were selected from approximately 3,000 with suspected viral disease from whom specimens were tested in the encephalitis battery (western encephalitis, St. Louis encephalitis, polio, herpes and others). On the basis of an earlier study,[3] it was estimated that diagnosis of a specific viral agent could be confirmed in half of the 3,000 cases. Clinical history was included

TABLE 1.—*Number of leptospirosis cases by year and source of report, California, 1961 to 1965*

Source	*1961*	*1962*	*1963*	*1964*	*1965*	*Total*
Reported to state	3	2 (1)	5 (1)	5	6 (1)	21 (3)
Serum survey	1	N.A.	5	5	7	18
Totals	4	2 (1)	10 (1)	10	13 (1)	39 (3)

N.A. — Serum not available
() — fatalities

with the transmittal form received with specimens from each of the approximately 1,500 remaining cases, and 540 were selected.

Selection was based on criteria proposed for an arbovirus study. The patient was selected when the history indicated aseptic meningitis and encephalitis primarily, or some fever of undetermined origin (FUO). The case was taken for study when paired sera were in good condition and definitely represented acute and convalescent periods, respectively, and routine serologic screening had failed to detect the agent involved. Almost half the survey patients were from the Central Valley (33 per cent from the San Joaquin and 12 per cent from the Sacramento Valley) and there were 22 per cent from the San Francisco Bay area. Fifty-five per cent of patients were infected in the period July through September, 57 per cent were under 20 years of age, and 55 per cent were males. In addition, viruses had not been recovered from stools or other materials submitted.

The sera were screened for the presence of leptospiral agglutinins with macroscopic slide test antigens obtained from the Biological Reagents Section of the National Communicable Disease Center (NCDC), using the method described by Galton and coworkers.[1] Sera which were positive in the slide test were sent to the Veterinary Public Health Laboratory, NCDC, for confirmation by live microscopic agglutination. Epidemiologic data were obtained on all suspected cases of leptospirosis.

Results

Twenty-one cases of leptospirosis, including three in which the patient died, were reported to

TABLE 2.—*Leptospiral agglutinin titers detected in 18 reported leptospirosis cases in California, 1961 to 1965*

		Clinical Phase		
Case No	*(Year)*	*Acute*	*Convalescent*	*Serotypes*
1	(1961)	1:128	1:256	*L. canicola*
2	(1961)	neg.	1:10,000	*L. canicola*
3	(1961)	N.D.	1:640	(1)
4	(1962)	1:512	>1:2,048	*L. canicola*
		1:2,048	>1:2,048	*L. icterohemorrhagiae*
5	(1963)	1:100 (2)		*L. pomona*
*6	(1963)	1:1,000	1:10,000	*L. canicola*
		neg.	1:1,000	*L. icterohemorrhagiae*
7	(1963)	neg.	1:100	*L. icterohemorrhagiae*
		1:1,000	1:100	*L. canicola*
8	(1963)	N.D.	1:400	*L. pomona*
9	(1964)	1:100	neg.	*L. canicola*
		neg.	1:50	*L. ballum*
		1:50	neg.	*L. grippotyphosa*
10	(1964)	1:50	neg.	*L. grippotyphosa*
		neg.	1:50	*L. canicola*
		neg.	1:50	*L. pomona*
11	(1964)	1:100 (2)		*L. pomona*
12	(1964)	1:400	1:100	*L. canicola*
13	(1964)	1:50	neg.	*L. ballum*
14	(1965)	neg.	1:50	*L. pomona*
15	(1965)	neg.	1:450	*L. pomona*
16	(1965)	1:200	1:800	*L. pomona*
17	(1965)	1:400	N.D	*L. canicola*
		1:100	N.D	*L. icterohemorrhagiae*
18	(1965)	neg.	1:50	*L. icterohemorrhagiae*
		neg.	1:100	*L. pomona*

(1) Macroscopic slide test results using *L. ballum*, *L. canicola*, and *L. icterohemorrhagiae* antigens.
(2) One serum submitted. Not known whether acute or convalescent.
*Fatal case.
N.D. Not done.

TABLE 3.—*Reciprocal of leptospiral microscopic agglutination titers detected in serum survey in California, 1961, 1963 to 1965*

Case No	Stage of Illness	Serotypes*								
		bal	*can*	*ict*	*gri*	*pyr*	*aut*	*pom*	*wol*	*ba*
1	A		(1)							
	C		200							
2	A			50				50		
	C									
3	A									
	C		100							
4	A									
	C								100	
5	A									
	C				50					
6	A		50	50						
	C									
7	A		100							
	C		200							
8	A									
	C		200	100						
9	A									
	C							50		
10	A							50		
	C							100		
11	A		50	50		50				
	C	50	100	50		100				
12	A	200	200							
	C	100	200							
13	A	100						100	100	
	C	200					200	400		
14	A									
	C	50	50							
15	A									
	C						20	100		
16	A			50			400	400		100
	C			50			400	400		
17	A			100			100			100
	C			1,600			200			400
18	A									
	C						50	100		

(1) Insufficient quantity to test. Was negative by macroscopic slide test.
*Serotypes: bal—*L. ballum,* can—*L. canicola,* ict—*L. icterohemorrhagiae,* gri—*L. grippotyphosa,* pyr—*L. pyrogenes,* aut—*L. autumnalis,* pom—*L. pomona,* wol—*L. wolffi,* ba—*L. ballico.*

the California State Department of Public Health during 1961-1965, and with detection of 18 more cases in the survey of sera from 1961 and 1963-1965 cases, a total of 39 known cases of leptospirosis was reached during the five-year period (Table 1). Diagnosis of the reported cases in 18 instances was based on serologic tests in addition to clinical findings (Table 2). Among the three remaining reported cases, diagnosis was made by isolation of leptospires from blood and urine (in a non-fatal case), by isolation from blood as well as silver stained sections of autopsy material in one fatal case, and by silver stained sections in another. Confirmation of leptospirosis in the serum survey was based on a change (rise or fall) in microscopic agglutination titer of one dilution or greater between acute and convalescent specimens with a minimum titer of 1:50 (Table 3). In some instances (Cases 11, 12, and 16) there was no detectable change in titer for one or more sero-

TABLE 4.—*Diseases suspected among leptospirosis cases detected in serum survey, California, 1961, 1963 to 1965*

Suspected Disease	*Number of Cases*
Meningitis (five cases)	
Aseptic	2
Virus encephalitis	1
Coccidoidal virus encephalitis	1
Undifferentiated	1
Encephalitis (nine cases)	
Viral	4
Meningo — coccidioidal or viral	1
Meningo — Coxsackie	1
Undifferentiated	3
Coxsackie	1
Fever of unknown origin	1
Western encephalitis, Q fever, psittacosis	1
Not given	1
Total	18

TABLE 5.—*Age and sex distribution of leptospirosis cases, California, 1961 to 1965*

Source	Sex	0-9	10-19	20-29	30-39	40-49	50-59	60 +	Total
Reported to state	F				1 (1)	1	1	1 (1)	4 (2)
	M			3	5 (1)	6	2	1	17 (1)
Serum survey	F				2				2
	M	1	7	3	1	1	2	1	16
Total		1	7	6	9 (2)	8	5	3 (1)	39 (3)

() — fatalities

types, yet a diagnosis was possible due to changes in others. Encephalitis or meningitis was the disease suspected in 14 instances (Table 4).

The 39 patients, six of whom were females, ranged in age from six to sixty-six years (Table 5). Eight of 18 patients in the serum survey were children although no children were among the reported cases. Ten of the reported cases were from the Los Angeles Metropolitan area and two from the San Joaquin Valley whereas in the serum survey there were, respectively, one and eight cases from those areas (Table 6). The number of serum-survey positives from each area reflects the number of patients tested from the given area. Leptospirosis was most prevalent during July, August and September among reported and survey cases (Table 7).

Thirty of 39 persons had had some known contact with animals, cattle and dogs being the most common (Table 8). Two persons had histories of swimming, one in a creek and the other in an irrigation canal, but no direct animal contact. A possible source of infection could not be determined in seven instances. Exposure related to occupation was considered in 12 cases (Table 9). A butcher was included, although a butcher's exposure potential would be slight unless he were an abattoir worker with possible exposure to contaminated urine or infected kidney tissue. In the case of two customs inspectors in the group, exposure of one might be considered related to occupational risk (contact with rats aboard ships). The other inspector worked at an airport and the only known animal contact was with a cat at home.

Discussion

It is evident from the serum survey that leptospirosis should be included in the differential diagnosis of CNS disease of suspected viral origin. The list of suspected diseases suggests lack of clinical features which would distinguish CNS disease due to leptospires from similar syndromes caused by other agents.

A detailed history regarding possible contact with animals or swimming in contaminated waters should aid in determining whether or not the disease might be leptospirosis. There was obvious occupational risk in less than one third of the cases, and therefore questions concerning animal contact limited to occupational risk would be insufficient in most instances. The absence of children among reported cases may reflect a tendency to consider leptospirosis an occupational hazard.

Leptospirosis can occur during any season. However, most cases were in the warmer months,

TABLE 6.—*Geographic distribution of leptospirosis cases occurring in California, 1961 to 1965 by source of report*

Area	Source of Report: Reported to State	Serum Survey	Total
Los Angeles Metropolitan	10	1	11
San Joaquin Valley	2	8	10
Sacramento Valley	3	3	6
San Francisco Bay	3	5	8
Other	3	1	4
Totals	21	18	39

TABLE 7.—*Seasonal pattern of leptospirosis cases occurring in California, 1961 to 1965 by source of report*

Season Calendar Quarter	Source of Report: Reported to State	Serum Survey	Total
Jan. - Mar.	4	1	5
Apr.-Jun.	4	2	6
Jul. - Sep.	9	14	23
Oct. - Dec.	4	1	5
Totals	21	18	39

TABLE 8.—*Possible sources of infection among 39 leptospirosis cases, 1961 to 1965*

	Number of Cases
Contact with Animals	
Cattle	14
Dogs (healthy)	13
Dogs ("sick")	4
Cats	5
Horses	3
Rats	5
Swine	3
Deer (hunter)	1
Contact unknown, but with history of swimming	
In canal or irrigation ditch	2
In creek	1

TABLE 9.—*Occupations of 39 patients with leptospirosis, 1961 to 1965*

	Number of Cases
Occupations with animal contact	12
Farmer-Rancher	5
Abattoir worker	2
Veterinarian	2
Butcher	1
Meat inspector	1
Milker (dairy)	1
Occupations unrelated to animal contact	27
Student	8
Housewife	5
Customs inspector	2
Machinist	3
Brewery worker	1
Carpenter	1
Hospital orderly	1
Jail inmate	1
Paper goods salesman	1
Policeman	1
Railroad fireman	1
Restaurant owner	1
Retail clerk	1

paralleling the peak of activity for a number of viruses. Therefore, a flurry of CNS cases may be leptospirosis resulting from exposure to some common source such as a contaminated swimming hole rather than viral disease.

Although leptospiral infections usually involve the CNS without signs of jaundice, classic Weil's disease does occur occasionally. Three fatal cases were reported during a five-year period, making a case-fatality rate of 7.7 per cent.

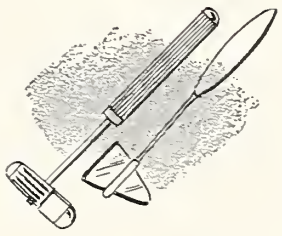
Titers of 1:50 or greater were found for the following Leptospira serotypes: *L. ballum, L. canicola, L. icterohaemorrhagiae, L. grippotyphosa, L. pomona, L. pyrogenes, L. autumnalis, L. wolffi,* and *L. ballico.* The former five serotypes have been isolated in California.[2] Agglutination tests for leptospirosis in California should include at least these nine serotypes. Of course, there may be other serotypes present which have not been identified. Evidence for the occurrence of the latter four above is only suggestive on a serologic basis without actual isolation.

REFERENCES

1. Galton, M. M., Menges, R. W., Shotts, E. B. Jr., Nahmias, A. J., and Heath, C. W., Jr.: Leptospirosis, PHS Publication No. 951, U.S. Government Printing Office, Washington, 1962.

2. Hubbert, W. T.: Leptospirosis in California: Diagnostic and Epidemiologic Problems, P.H. Reports, 82: 429-433, 1967.

3. Magoffin, R. L., and Lennette, E. H.: Nonpoliomyelitis viruses and paralytic disease, Calif. Med., 97:1-7, 1962.



San Francisco Stakes a Claim

ONE HUNDRED YEARS AGO

MARY E. MATHES, M.D., *San Francisco*

ON THE HUNDREDTH anniversary of the San Francisco Medical Society, the first medical organization in the West which has been in continuing existence since its beginning, it is of interest to look back over the early struggles that led to its founding. The Society was not formed in the routine of a settled community. Its roots extend back into the hectic boom days when an isolated, sparsely populated land that knew little of law and order was suddenly inundated by a horde of avid gold seekers.

It was by pure chance that Marshall picked up yellow particles from Sutter's millrace just when this western territory was being wrested from Mexico. California's spectacular rise on the American scene was founded upon luck, pure gold, an agreeable climate and arable land—a combination of virtues which practically insured permanence. When the word *gold!* rang across the states the rush was on. Never was a new and unprepared country so rapidly populated. Amid the motley throng there was a surprisingly large number of doctors, an estimated 1,200 to 1,500 at the height of the rush. The only things they had in common were that they were young and imbued with a spirit of adventure and their thoughts (as a rule) were of gold rather than of medicine. Very few attained the goal of wealth. Gold was not to be picked up as they walked along. Unaccustomed hard physical labor and wretched living conditions sent many home (if they could find the money for boat fare).

Others turned to medical practice in the area—or in San Francisco. These were the men who, in the isolation of the Far West, began to feel the need for better rapport in the profession. The first medical society in northern California was founded in the hub of the mining country when 50 enthusiastic doctors met in Sacramento 4 May 1850. A few weeks later the hustling port city of San Francisco gave birth to the San Francisco Medical Society.

As its first activity the San Francisco group set out to establish a standard for medical fees. This proved to be a fatal mistake. Arguments over the fees proposed and the necessity to abide by any set fee occupied the meetings and ended with the complete disruption of the organization after four months of wrangling. The Sacramento Society led a more harmonious life but died of inanition after a few years. Efforts to organize the profession, however, did not die with these first societies. Two subsequent groups in Sacramento and three in San Francisco appeared during the decade. All of these organizations after auspicious beginnings dwindled and by the early 1860s ceased to exist.

The diverse backgrounds of the early medicos, their strong individualism and constantly shifting numbers militated against harmony. The final blow to early organization would seem to have been the bitter personal animosities aroused by the Civil War.

Not a single medical organization had existed in the state for some six years when the doctors of San Francisco organized the present society on the fourth of February 1868, a full hundred years ago. A few weeks later the Sacramento Society for Medical Improvement (the present Sacramento County Medical Society) held its first meeting in Sacramento.

Great changes had been wrought in California over the 20 years that had elapsed since the discovery of gold. Gold fever was being replaced by an era of permanence and stability, the West had become "home" to increasing numbers instead of a temporary Mecca for fortune hunters. Fertile

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Reprint requests to: San Francisco Medical Society, 250 Masonic Avenue, San Francisco 94118.

fields were tilled, bumper crops were harvested in '68. Industries flourished, business houses, churches and schools were founded. The telegraph had established a link of rapid communication with the East. The approach of the transcontinental railroad stimulated business and triggered a boom in real estate.

San Francisco now had a population of nearly 150,000, a decent water supply had been brought in, and there was a public library, a medical school (Toland), theaters, an opera house and a number of permanent buildings and houses. The atmosphere of this prosperous year boded well for the new medical society.

The organization of the group once started, proceeded with the dispatch of long practice (this being the fifth society formed in San Francisco). The objects of the Society were pertinent and simply stated: One, the advancement of medical knowledge, had a special meaning for the isolated westerners. There was no medical library, a paucity of books, and periodicals were months old when they arrived. Founding of a library was definitely planned, as shown by the appointment of a librarian at the start, long before there was a book upon the shelf. The second objective was the familiar one —to promote union and harmony, but in addition to elevate the standards of medical education. The third *raison d'etre* was to separate the regulars from the irregulars. This was an important consideration at a time when no license was required to practice medicine. Anyone so inclined could hang out a shingle and advertise his skills in the newspaper. San Francisco abounded in such quacks. A few years later medical organization proved its worth in an active campaign that culminated in the passage of the Medical Practice Act of 1876. Even so, it nearly destroyed itself in a feverish quack hunt under the new law.

The code of ethics adopted was that of the National Medical Association (as the forerunner of the American Medical Association was called). The code devoted a long article on the "Obligations of Patients to their Doctors," which today has an amusing appeal. In the article, patients were warned as follows: They must (1) Give a complete history with no reservations; (2) Never weary the doctor with tedious details; (3) Follow the doctor's advice faithfully and reject advice and medicine from others; (4) Notify and present the reasons for changing physicians; (5) Always (except in emergency) send for the doctor in the early morning before he starts on his rounds (by horse and buggy, of course) and not call unnecessarily during the hours of meals or sleep.

No mention of a fee schedule is to be found—the doctors had learned their lesson from sad experience.

The scientific meetings were held twice monthly at the old City Hall in the rooms of the 12th District Court (by courtesy of Judge O. C. Pratt). The only expense entailed was 75 cents a night for the janitor. In September the meetings were moved to more comfortable quarters in a hall on Market Street for which the Society paid $2.50 a night. This proved a lucky move, for in October a severe earthquake shook the venerable City Hall so hard that it had to be vacated for a year during repairs. Notices of the meetings were sent by a messenger who received $1.00 to deliver each lot of 50, until house-to-house mail delivery was instituted a year later. Telephone service was yet a decade away.

The founding membership of 23 soon increased to 42 and by the end of the year there were 48 members, representing only about one-fourth of the regular physicians in San Francisco.

What did our Society discuss a hundred years ago? The programs were most informal. A few well organized papers were interspersed with case reports and spontaneous discussion on various topics. Cholera was expounded upon at length, with tall tales of experiences here and abroad, several doctors insisting that the disease was not contagious. Complications of obstetrics were presented in gory detail. The subject of aneurysm and circulatory disease occupied several meetings and brought forth some excellent scientific discussion. Outstanding was a paper read by Dr. Arthur G. Soule (visiting physician to the City and County Hospital) based upon 50 cases of aneurysm he had seen over a three-year period and on which he had recorded complete histories and records including postmortem examinations. The statistics from the local Board of Health showed the death rate from aneurysm in San Francisco to be nine times that of New York. Speculation as to the reason for this high included "the mode of life in this new land," such as poor diet and living conditions, heavy work and heavy drinking.

Presentation of specimens seemed to be a popular feature on the programs, many more or less fresh specimens from interesting cases were brought to meetings for the edification of the as-

sembly. No wonder the Society's first purchase was a wash basin and stand!

An epidemic of smallpox broke out midyear. The rapidly increasing morbidity and high mortality of the virulent disease claimed the attention of the Society for the rest of the year. The members had no time to chase quacks or argue over ethics. A committee from the Society undertook a survey of the facilities (or rather, lack of facilities) available for the isolation and care of smallpox cases. They produced a very complete study including a list of practical suggestions and a sketch of plans for a new isolation hospital to augment the inadequate quarters of the old pesthouse. The report was presented to the city's Board of Supervisors, where Dr. Beverly Cole (a Society member and chairman of the city Hospital Committee) received it with open arms. Most of the recommendations, including the new building, were implemented.

A glance at the equipment available to the physician of 100 years ago shows a startling contrast to our present age of "mechanized" medicine. Most doctors possessed a stethoscope; a stylish physician carried a gold-plated one. Thermometers were expensive and scarce—anyway, who needed a thermometer to judge a fever? If need be, one could be made by removing the metal scale of an ordinary thermometer and calibrating the glass. Hypodermic administration of drugs had been in vogue for several years, now that the syringe had become cheap enough that most physicians could possess two. Leeches were still in use but a cannula for bloodletting was used more commonly. The laryngoscope and endoscope were just coming into use, but it was difficult to secure proper lighting in the absence of sunlight—flickering candles and gas light were difficult. Further innovations included the vaginal speculum and the means for urinalysis. The doctor's bag contained a scant handful of surgical instruments — not sterilized, of course, as germs were still unknown. Most of the physician's equipment lay within himself, the keenness of his perceptive senses plus the extent of his experience.

Although no affiliation existed between local medical societies and the National Medical Association, the annual national meeting was attended by many representatives of assorted medical groups, including hospitals. Several members of the San Francisco Medical Society received notice of the annual meeting to be held in May of 1868 in Washington, D.C., but no delegate was sent—the meeting was already over by the time the notices had reached the Coast. Soon after this, Dr. Henry Gibbons, Sr. (a charter member of the National Medical Association) received word that the national group would like to meet in California in the near future after the transcontinental railroad was completed. Since there was no state medical society in existence at the time, Dr. Gibbons took it upon himself to extend an invitation in behalf of the doctors of California with an assurance of a hearty welcome. The prospect of hosting a national convention proved to be an important stimulus to medical organization in the coastal states. The California State Medical Society hastened to reorganize and new county societies bloomed out. The meeting, which was held in 1871 in San Francisco, was hailed as a success and was notable as probably the first time the doctors of California had worked in relative harmony.



The "Carrier" in Government Medical Care Plans

RICHARD S. WILBUR, M.D., *Palo Alto*

PASSAGE OF THE Medicare and Medicaid law in 1965 drastically altered our whole system of medical care. An integral part of this same law, P.L. 89-97, was the use of what the law calls a "carrier" to handle the means of payment for those who provide services under these medical care plans. What is a carrier, and who needs it? Is there really any need for this third party—this middleman—this extra step and expense in the already complex relationships between government and the providers of service?

The carrier specified by P.L. 89-97 must be a private organization, with previous experience in handling prepayment health care plans. It must have covered a significant number of policy beneficiaries in the area it is to serve. Its function is to supervise the proper distribution, subject to government regulation and audit, of the health care funds of the program. These are distributed to the providers of service — the physicians, dentists, druggists, optometrists and all others who care for patients, or to the beneficiaries (the patients) as under Medicare.

The first reason for using the carrier is simply that the necessity of setting up these enormous programs in a short period demanded the use of a preexisting mechanism. The administration of Medicare directly by government would have required the establishment within a year of a massive new bureau composed entirely of people with little or no experience in the processing of health care claims. The alternative of turning to experienced private enterprises with a long history of handling such claims on a private basis meant that the program could be initiated sooner and with far less difficulty. The use of a carrier by government was not a new idea with P.L. 89-97. For instance, California Physicians' Service worked successfully in similar functions under various government programs since World War II.

In California, Blue Shield (CPS), both Blue Cross Plans and the Occidental Insurance Company all had qualified managers and supervisors to train the newly hired personnel needed by expansion. These key people, who knew claims processing, were able to train newly hired clerks in a way in which no state or federal government agency could possibly have done.

Not all government agencies chose to use this efficient system, unfortunately. Whereas in California, Blue Shield implemented the Title XIX Program for the entire state with the addition of 1,300 employees, New York City attempted to implement its Medicaid Program by the use of its own welfare department, and for that one city alone hired 3,000 new employees. California Blue Shield pays the vast majority of Medi-Cal claims within a period of 30 days, while New York City is still attempting to pay claims within a period of less than six months, and has finally begun negotiating with the local Blue Shield Plan to straighten out its problems.

The use of an already existing mechanism not only leads to the rapid institution of efficient and economical claims processing, but makes use of personnel who have developed knowledge from long experience with patterns of practice, and with reasonable costs and charges. They are able, as well, on a continuing basis, to compare those fees submitted under government-financed plans with those from their standard business. Usual and customary fees could not be implemented by a government bureau, for it would not only be inexperi-

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Reprint requests to: 300 Homer Avenue, Palo Alto 94301.

enced in claims processing, but would also lack a background of fee evaluation experience to draw upon. Thus the use of the carrier eliminated the need for a fee schedule at the inception of both Medicare and Medi-Cal. Furthermore, the use of the carrier means that one private organization, which handles its own standard commercial program in addition to Medicare, Medi-Cal and the CHAMPUS† Military Dependents' Program, may use the experience from each as a measure for the others. This not only provides a valuable cross-check, but at the same time removes the necessity for each of three different branches of government to develop large, new, duplicate staffs of civil servants to process health claims.

A buffer is defined as a soft object which absorbs the shock of a collision between two harder objects. This is the role of the carrier—to act as a buffer between government and the "provider of service."

Advantages for Government

The presence of the carrier has advantages for both parties. For the government it removes the need for a new bureau which, once it had attained full growth, probably would be rigidly fixed in size. Blue Shield operates on a 30-day-cancellation contract under Medi-Cal, and a year-to-year contract under Medicare. If performance by the carrier, is unsatisfactory, the government may simply change to a different one, without encountering the almost impossible task of dismantling a large civil service bureau. The advantage to government of the efficiency of claims processing by experienced personnel has been noted already.

Another advantage to government is the fact that there need be no direct dealings with the various providers. Since the government agencies have had no such dealings in the past, misunderstandings would be even more common if carriers were not used. The resultant communications (some of which might be expected to be vituperative) would also be distributed to the Legislature and Congress, as well as to the Executive Branch, with further headaches for the agencies. When using carriers, there are also fewer direct dealings by government with the program beneficiaries, which reduces the chances of similar misunderstandings.

For the government and the taxpayer, a carrier is valuable as an organization which has a genuine interest in keeping down the cost of the programs since any increase in health care costs is also reflected in the carrier's own standard insurance programs. No carrier that did not have a significant amount of standard business with which to be concerned was selected under Medicare.

A similar advantage to government, particularly in the case of Blue Shield, has been the existence of a well-functioning, active, and aggressive peer-review mechanism — the medical advisors, and medical society county review committees. This too insures a further careful surveillance and control of health care costs.

Advantages for the Provider

One advantage to the provider of services is that he need not deal directly with the government. No single provider can ever feel anything other than smothered by the very size of government. With the help of the carrier, however, he can have his problems heard and make his protest felt, since the carrier has a friendly ear — Blue Shield is most anxious to maintain excellent physician relations, and will defend and protect the provider of service as well as the patient.

Another advantage to the provider is that he deals with the same office and the same people, through long established mechanisms, for all of his claims problems, government and private. He does not need to deal with many different systems. The forms devised by the carrier are simple and are similar to those he has used for years, quite different from the complicated ones devised by less experienced persons in government—for example, CHAMPUS.

Again, the carrier has knowledge of the cost payment statistics. Therefore, when it happens that figures are published, such as those alleging 1,200 California physicians had received $70,000 apiece from Medi-Cal, the carrier is in a position to refute the allegation and to release the facts. This would be impossible if only government agencies had access to these statistics.

An advantage for both parties is that the carrier is an interpreter of government regulations to the provider, and vice versa. Much time has been spent by many officials of Blue Shield discussing with government officials the reasons why some apparently logical ways of economizing on physicians' payments would do nothing more than harass already overworked doctors without

†Civilian Health and Medical Programs, U.S.

in any way improving the quality of care or lowering the program cost. Much more time has been spent trying to make government regulations intelligible to those who actually deliver health care.

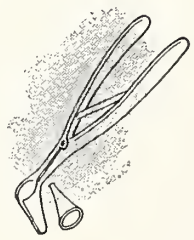
Problems of the Carrier

The role of a buffer is not an easy one, nor did anyone expect it to be. In California, Medi-Cal has presented enormous problems — such as that of attempting to find out from the state which patients are actually eligible for welfare medical benefits. After two years this is still not satisfactorily resolved. Other problems include the task of explaining the programs to physicians who did not see the need for such a law in the first place, the enormous size of the programs, and the almost incredible amount of correspondence made necessary by both the size and the complexity of Medi-Cal. These are only four of many. Taken altogether, they have made many persons working for Blue Shield less happy about the use of a carrier than is either of the other two parties.

For all of these reasons, Blue Shield is vitally interested in constantly improving the Medicare and Medi-Cal Programs, many features of which were enacted without sufficient research and experience.

Through the strong link with the California Medical Association, Blue Shield is deeply interested in quality medical care, whether privately or government financed. Blue Shield is also interested in claims cost stabilization. Since some inflation in costs is inevitable with the rises in salaries of office nurses, laboratory technicians, x-ray technicians and the like, health care cost control will have to come through new and better ways of delivering this health care, rather than simply by arbitrary attempts to limit fee payments. Blue Shield is helping to finance some of these studies and the Blue Shield Research Department has already made a number of suggestions, several of which have been implemented and more of which are ready to be instituted. Because of its interest, its experience and its capable personnel, Blue Shield is better able to innovate improvements than is any government agency. The present system is far from ideal, but as long as free enterprise is represented by the carrier, the physician has a strong mechanism through which he can lead the way to constantly improving these government programs. The carrier will act as a catalyst in the developing of new and better ways of providing health care for the people of the United States.

Who needs the services of a carrier? Everyone — government, physician, taxpayer and patient.



The Rural Health Program of Southern Monterey County

LEN HUGHES ANDRUS, M.D., *King City*

■ *The Rural Health Project of Southern Monterey County is attempting to demonstrate that a private group of physicians with the collaboration of the County Medical Society can responsibly and efficiently conduct a program of providing comprehensive medical care to indigent patients.*

Within the purposes of P.L. 89-749, the Rural Health Project is experimenting with a new way of organizing indigent health care and at the same time is providing the basis for comprehensive health planning at the local level.

THE OFFICE OF Economic Opportunity (OEO) is sponsoring 41 community and neighborhood health projects across the country (at a cost in 1967 of approximately fifty million dollars) which are aimed at providing medical care to poor people. The projects are situated in 32 different areas of 20 states. Four out of five projects are located in urban areas. Most are being conducted by community action agencies, poverty councils, health departments, hospital medical centers or medical schools. Three are connected with prepaid health plans (Kaiser in Portland, Oregon, Medical Foundation of Bellaire, Ohio, and Mound Bayou Community Hospital in Mississippi) and three are associated directly with medical societies (Fulton County Medical Society in conjunction with Emory University School of Medicine in Atlanta, the Provident [Negro] Medical Society in Brooklyn, New York, Lowndes, Alabama, and our own project in Southern Monterey County). Such projects are attempting to carry out one of the aims of comprehensive community health planning by demonstrating how Title XIX activities can be coordinated with existing health programs in our communities. Furthermore, data are being gathered which will aid in the planning of health services.

Public Law 89-749 stipulates that a majority of the members of state health planning councils shall be "representative of consumers." OEO grants also require that consumers participate in health planning. We accept this concept, but add three other essential ingredients to community planning: (1) The need for the private medical practitioner's voice in community health planning; (2) A leading role for the county medical society; and (3) The assurance that the evaluation of medical care is part of the planning.

Submitted 27 December 1967.

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The author is Project Director for the Rural Health Project of Southern Monterey County, King City, California. The project is sponsored jointly by the Monterey County Medical Society and by the Southern Monterey County Medical Group. In addition to Dr. Andrus, other members are: Deane T. Brooke, M.D., Associate Project Director; Lee S. Roberts, Clinic Administrator; Edgar H. Colvin, Executive Secretary, Monterey County Medical Society; Jerome L. Schwartz, Dr. P. H., Medical Care Consultant, and Richard V. Bibbero, President Medical Management Control. This project is supported by Demonstration Grant No. CG9682 from the Community Action Program, Office of Economic Opportunity.

The Rural Health Project

The Rural Health Project of Southern Monterey County is unique because it combines all four of these elements: It represents the only community demonstration project sponsored by a medical society and conducted by a private medical group. We believe that the private sector of medicine should recognize the health needs of the community and take the initiative in meeting these needs. In those areas where it is impossible to meet the needs on the free enterprise or open market basis, then private medicine should seek assistance of the government and with governmental support and cooperation aggressively try to solve these health problems and maintain the reins of leadership.

The grantee for the Rural Health Project is the Monterey County Medical Society. The delegate agency is the Southern Monterey County Medical Group with offices in Greenfield and King City, California. The George L. Mee Memorial Hospital and the Pioneer Hacienda Nursing Home are collaborating agencies in the project. The application was supported by the county Community Action Program, the State and County Health Departments, the State Director of Anti-Poverty Planning, State Legislators and Federal Congressmen.

The program had its inception long before P.L. 89-749. In trying to meet the needs of the medical indigents of our area, the Southern Monterey County Medical Group had developed a plan for a pilot study to be underwritten by the Board of Supervisors of Monterey County. Our pilot study proposal was precluded when legislation at both the Federal (Title XVIII and Title XIX) and State (Casey Bill-AB 5) levels provided broadened programs to finance medical care for the needy. At this point we developed an application for a health demonstration grant funded by the Office of Economic Opportunity.

The Rural Health Project is designed to demonstrate the provision of comprehensive medical, surgical, hospital and other health services, through organized private group medical practice. The target population consists of about 800 poor families and an undetermined number of non-resident migrant farm workers. In the past these families have either lacked medical care completely or depended largely on the distant county hospital, 50 miles north of King City and 85 miles north of the southern boundaries of the county.

The project is identifying and serving all poor families in the area. "Health Aides" have been recruited from the eligible population itself and are being used to establish communication with the target population. They also serve as vital links between the needy and the service, the server and the served.

A research component is embodied in the project plan. Monies available from various sources to pay for care are identified and placed in a "pool." Funds committed for medical care from any source (such as Medicare, Medi-Cal and the Crippled Children program) will be paid back to the project in those cases where patients are eligible for them. All services and claims will be analyzed to provide valuable data for planning other health service for low income and indigent families.

Staffing and Training Phases

The use of public health and social welfare professionals in a private group and the feasibility of providing careers in the health field to members of indigent families are also being demonstrated.

Public health professionals added to the group's staff under the grant include a public health physician, a public health nurse and a health educator. Other professionals are two social workers and a community coordinator. The grant led to enlargement of our staff by adding several physicians, a registered nurse and an occupational therapist. A medical care specialist and statistician are providing technical assistance, particularly in the research and evaluative aspects of the project. Funds have also permitted us to expand our computer equipment and to lease three small buses. Recently we received approval to convert a motel near the office and hospital into an intermediate care facility. We are seeking a public health nurse and we hope in the future to broaden the program to include dental and mental health care.

An important aspect of the program is the training of persons from poor families—some with only grade school educations—for careers in the health field. In rural areas in particular, there are shortages of skilled health aides. When our project staff is at full complement, we will be training 35 aides in 14 different phases of our program. The wide scope of the training program is revealed from the various kinds of aides to be employed: physical therapy trainee, occupational therapy trainee, x-ray trainee, laboratory trainee, IBM trainee, medical secretary trainee, medical clerk trainee, social

work aide, home health and language aide and transportation aide. Twenty aides will be trained in the fields just mentioned, and the other 15 will be trained in three subprofessional nursing positions—clinic nursing aide, hospital nursing aide and nursing home aide. This experience in training persons from the indigent population has been one of the most exciting and rewarding functions of our project.

Home Health Care Agency

We have the necessary components of a licensed Home Health Care Agency, a physician, medical director, public health nurse, social worker, public health nurse and social worker, and the additional personnel of a physical therapist and an occupational therapist. We are already using the Home Health Care Agency personnel extensively and not only hope to demonstrate its value in service to patients but also that it can be a self sustaining if not a profitable function of a private medical group.

Problems and Accomplishments

The project has been in operation for only four months. It is notcworthy that the government has granted us complete autonomy to administer the project as we see fit. Although we have accomplished a great deal in this short period, we have had somc difficult problems. The major problems havc been shortage of physicians, lack of sufficient space, difficult policy determinations, coordination of the project with the clinic, hospital, nursing home, motel and consultants, the establishment of a five night per week evcning clinic to 10:00 p.m., resistance among our personnel, the training of a large number of aides, broken patient appointments, and education of the target population to proper utilization of medical facilities.

The government may have been reluctant at first to permit a private group of physicians to establish and operate a community program for indigents. Most other grantees are non-profit groups or governmental agencies. We have surprised many interested people with our speed in beginning to provide patient care. Our project began on 11 June and we began seeing patients 18 July. Only eight of the 41 community health projects, including our program, have begun serving patients.

We had distinct advantages, in that we were an ongoing medical group with facilities, equipment, a skilled staff and accounting-computer capability. Of course, the increased load of patients and the need to recruit additional staff has presented us the problems and forced us initially to limit the number of new patients. But we have been able to carry out some of the immediate steps of the project faster than community or government-sponsored grantees. We have also pre-tested and developed a social history form to provide data relating to demographic, social and health characteristics of our project patients. Another form which we have put into operation — The Patient Care Contact form—provides data relating to each patient contact with the project, including the reason for the visit, the medical diagnosis and the disposition of the case. We made some changes in our IBM system and will be able to analyze all medical, paramedical and hospital services provided to project patients in terms of the patient's social characteristics, medical diagnoses and costs.

We have established a mechanism whereby the Monterey County Medical Society, through a medical review team, is examining our records and claims. We are also performing an internal medical audit and a medical care specialist is reviewing our overall program.

CASE REPORTS

Carcinoma of the Thyroglossal Duct

Primary or Metastatic from the Thyroid?

ARTHUR O. WEBER, M.D., *Torrance*

TWENTY-FOUR CASES of carcinoma of the thyroglossal duct have been reported.[8] In all but two cases[1,5] the lesions were papillary adenocarcinomas, and in only two was there demonstrable metastatic tumor in regional lymph nodes.[3,4] None of the patients died directly from recurrence or spread of the carcinoma. Surprisingly, only two[1] of the reported patients were treated with concomitant thyroidectomy.[7,8] In no previous case was an associated carcinoma of the thyroid gland reported.

In the present case, an occult papillary adenocarcinoma of the thyroid was presumed to be a separate primary neoplasm and, as such, aroused special interest and speculation regarding therapy.

Report of a Case

The patient, a 23-year-old woman, was admitted to hospital 20 February 1966 because a firm, submental mass that had been present for as long as the patient or her family could remember had doubled in size—to 6 cm—within the preceding year. There was no history of inflammation.

On physical examination the mass could not be moved laterally but it moved up and down with swallowing. The surface was irregular, with one firm nodule 1 cm in diameter. The thyroid gland was small, symmetrical and smooth, without nodules. No other masses were palpable within the neck.

I^{131} uptake was 53 per cent in 24 hours, and an I^{131} scan showed uniform activity within the thyroid gland. There was no uptake outside the thyroid gland or over the submental mass.

At operation the mass was exposed with a long, transverse, elliptical incision and was found to be intimately fixed to the surrounding thyrohyoid, sternohyoid, digastric and mylohoid muscles. Without biopsy of a specimen the mass was excised in toto, including the muscles to which it was fixed and a 1-inch segment of the central portion of the hyoid bone. The pathologist* reported a frozen section showed mixed papillary and follicular carcinoma of the thyroid, infiltrating skeletal muscle. However, there also was a benign epithelial element, interpreted as showing origin within a thyroglossal duct cyst. (See Figures 1, 2 and 3).

An occult primary tumor within the thyroid gland was considered an outside possibility, inasmuch as no nodularity of the thyroid was palpable and the I^{131} uptake was uniform. However, it was felt desirable to ablate the thyroid totally, so that any recurrence might be identified by I^{131} uptake and then destroyed with I^{131} therapy. Total thyroidectomy was undertaken ten days after the initial procedure. No nodularity was palpable when the gland was exposed, and the only lymph nodes encountered in the sugical procedure were negative for tumor. However, on subsequent step cuts of the totally embedded thyroid gland, the pathologist† reported a 4 mm primary mixed follicular and papillary carcinoma (Figure 4).

Postoperatively, the small remnants of functioning thyroid tissue were ablated with I^{131} and thereafter the patient was given 0.26 gm of thyroid extract daily. It is planned that periodic scanning with I^{131} for any functioning thyroid tissue will be

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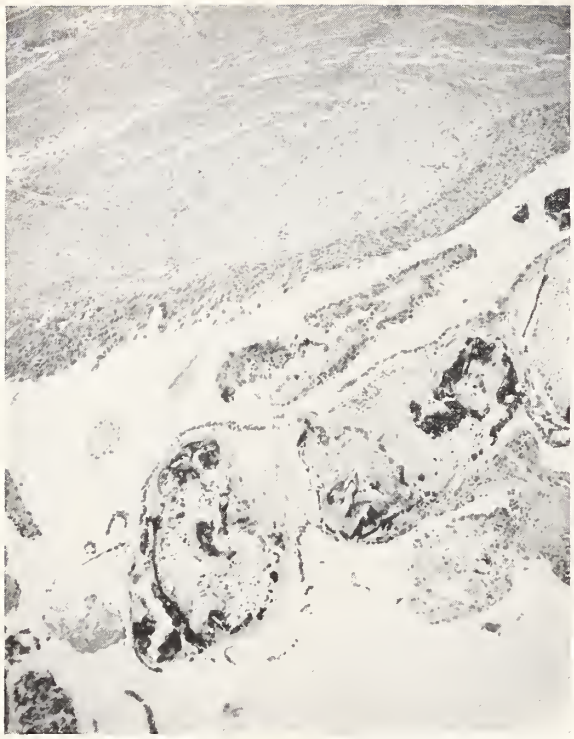


Figure 1.—Thyroglossal duct cyst wall and surrounding hyalinized papillary carcinoma (× 100).

carried out and any functioning thyroid again ablated with I^{131} (to date, two years after operation, there is no evidence of recurrence).

Discussion

Any rapid increase in size or a very large, nodular, fixed, submental mass may give rise to suspicion of carcinoma within a thyroglossal duct cyst. Failure of the mass to show any function with I^{131} scanning does not rule out the possibility of thyroid carcinoma within the thyroglossal duct cyst. If fixation or invasion of surrounding musculature is noted at operation, it would seem advisable to resect the lesion en bloc. However, most cases reported in the literature appeared to be "typical" thyroglossal duct cysts, and the correct diagnosis was made only after microscopic examination of the surgical specimen.

Although in the present case the interpretation was that there were two primary lesions, it is pertinent to note that Crile[2] said that the thyroglossal duct tract may be a route of spread of carcinoma of the thyroid. Nuttal[6] eloquently stated the possibility of confusing *cystic* metastasis from an occult

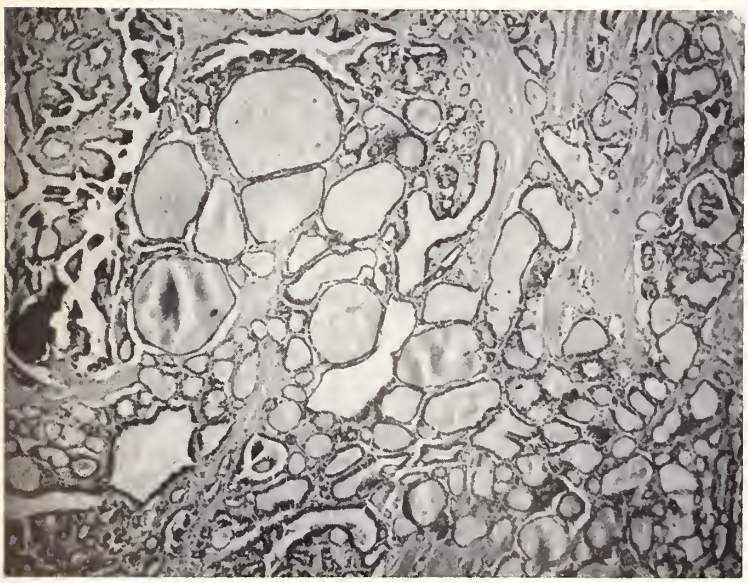


Figure 2.—Papillary and follicular thyroid carcinoma in thyroglossal duct remnant (× 100).

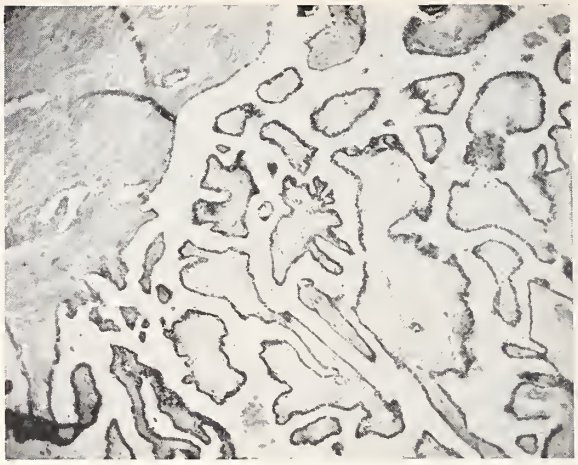


Figure 3.—Papillary carcinoma in thyroglossal duct remnant (× 100).

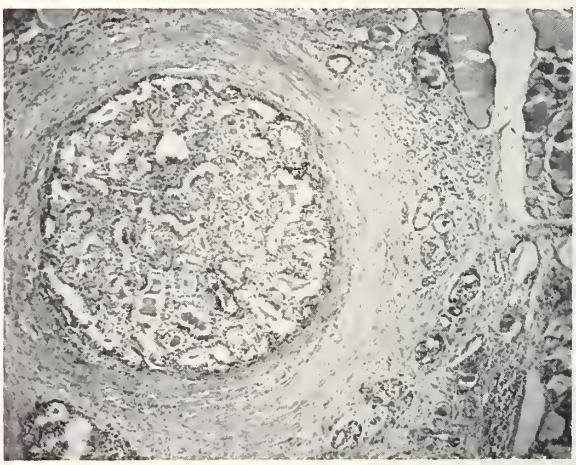


Figure 4.—Small primary papillary carcinoma in thyroid gland (× 100).

primary carcinoma of the thyroid gland with carcinoma originating within a thyroglossal duct cyst. Woolner and coworkers[9] reported upon two cases of occult papillary carcinoma of the thyroid in which a previous diagnosis of "carcinoma in thyroglossal duct cysts" had been made erroneously. On microscopic examination these cystic metastatic lesions, however, typically have a thin wall, with or without lymphoid tissue, which may be mistaken as evidence of thyroglossal duct cyst.

Some doubt may always remain whether the submental mass in the present case was a metastatic tumor. However, the history of the patient's having had a submental mass "all her life" and the microscopic evidence of a benign epithelial component are taken as strongly indicative that the submental carcinoma originated within a thyroglossal duct. One can speculate that whatever factor (perhaps excess thyroid stimulating hormone) stimulated carcinogenesis within the ectopic thyroid tissue may also have engendered the carcinoma within the thyroid gland itself.

Perhaps consideration should be given to total thyroidectomy in patients found to have thyroid carcinoma in a thyroglossal duct cyst, not only to rule out an occult primary lesion but also to make follow-up I^{131} scanning and ablation of recurrences possible. As the present case illustrates, an occult primary lesion may escape detection even on palpation of the thyroid gland at operation and gross examination by a pathologist. Thyroidectomy then would remain, in those circumstances, the only means by which an occult primary lesion could be demonstrated. Finally, suppressive doses of desiccated thyroid seem indicated.

Summary

The twenty-fifth reported case of carcinoma occurring within a thyroglossal duct cyst is reported. The presenting submental mass was somewhat atypical in that it was large—6 cm—and fixed because of invasion of surrounding musculature. This invasion made en bloc resection of these muscles necessary. A separate occult primary lesion was found within the thyroid gland. Total thyroidectomy seems advisable in the treatment of thyroid carcinoma occurring within a thyroglossal duct cyst, since the procedure would make subsequent I^{131} uptake studies, scanning and ablation of metastatic lesions possible.

REFERENCES

1. Clute, H. M., and Cattell, R. B.: Thyroglossal cysts and sinuses, Ann. Surg., 129:642, 1949.
2. Crile, G., Jr.: Papillary carcinomas of the thyroid and lateral cervical region, so called "Lateral Aberant Thyroid," Surg., Gynec. & Obst., 85:757, 1947.
3. Fish, J., and Moore, R. M.: Ectopic thyroid tissue and ectopic thyroid carcinoma, Ann. Surg., 157:212, 1963.
4. Keeling, J. H., and Ochsner, A.: Carcinoma in thyroglossal duct cyst, Arch. Otolaryngol., 75:89, 1962.
5. Marshall, S. F., and Becker, W. F.: Thyroglossal cysts and sinuses, Ann. Surg., 129:642, 1949.
6. Nuttall, F. Q.: Cystic metastasis from papillary adenocarcinoma of the thyroid with comments concerning carcinoma associated with thyroglossal remnants, Am. J. Surg., 109:500-504, 1965.
7. Rees, C. E., and Brown, M. J.: Cysts of thyroglossal duct, Am. J. Surg., 85:597, 1953.
8. Snedecor, P. A., and Groshonf, L. E.: Carcinoma of the thyroglossal duct, Surgery, 58:969-978, 1965.
9. Woolner, L. B., Beahrs, O. H., Black, M. B., McConahey, W. M., and Keating, F. R., Jr.: Classification and prognosis of thyroid carcinoma: A study of 885 cases observed in a thirty year period, Am. J. Surg., 102:354, 1961.

Prinzmetal's Variant of Angina Pectoris with Only Slight Coronary Atherosclerosis

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SINCE THE original report[3] of the syndrome which is now known as Prinzmetal's variant of angina pectoris, several observers[1,2,4] have published accounts of this interesting constellation of findings. Pathologic examinations in such cases have revealed decided arteriosclerotic narrowing of a large coronary artery.[3] In the case here reported, Prinzmetal's variant was associated with only mild atherosclerosis of the coronary arteries.

Arrhythmia frequently occurs during the is-

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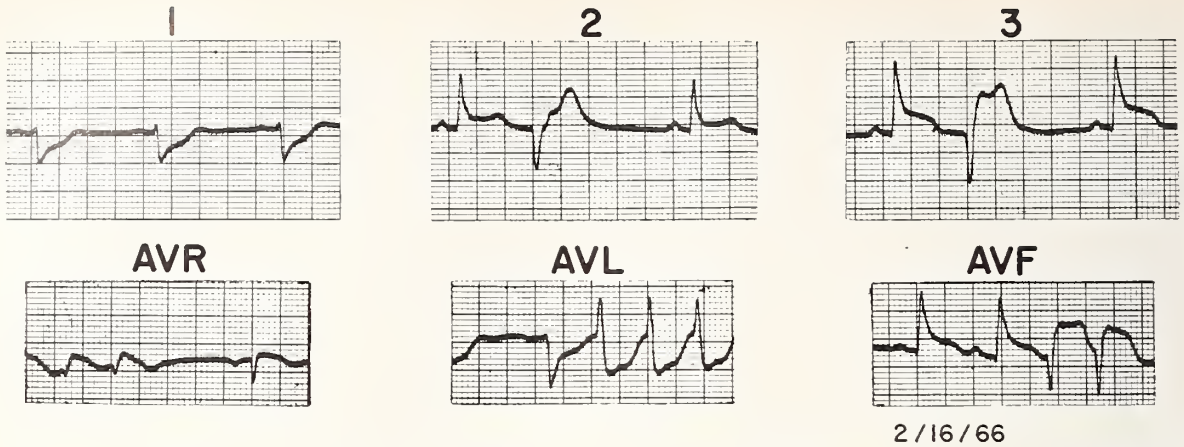


Figure 1.—Six-lead electrocardiogram taken during an episode of chest pain. It shows ST elevation in leads II, III and AVF. There are frequent premature ventricular contractions and in lead AVL three consecutive premature contractions (the criterion for ventricular tachycardia) are shown.

chemic episodes of Prinzmetal's variant.[3] Characteristically it takes place at the peak of a bout of chest pain, and it may be associated with syncope. In the present case, ventricular asystole and syncope necessitated implantation of an artificial pacemaker.

Report of a Case

A 49-year-old white woman was transferred to Palo Alto Stanford Hospital 24 March 1966 because of pain in the chest.

In 1955 she had her first episode of substernal chest pain. Thereafter she had four to six such episodes a year. The pain usually occurred at night and was not often related to exercise. In February 1966 the frequency and severity of the pain increased, and the patient entered a hospital. There it was observed that the ST segments in leads II, III and AVF were elevated during the pain, and there were associated paroxysms of ventricular tachycardia (Figure 1). In early March she had cardiac arrest which was successfully treated. Because of the intractable chest pain she was transferred to Palo Alto Stanford Hospital.

On physical examination at the time of transfer, blood pressure was within normal limits, the cardiac rhythm was regular with a rate of 80 and the heart sounds were normal. There was no evidence of cardiomegaly or of congestive heart failure. An electrocardiogram showed mild ST depression in the lateral precordial leads.

On the day of transfer the patient had a bout of severe chest pain followed by complete heart block with idioventricular rhythm at a rate of 30.



Figure 2.—Coronary arteriogram taken in left anterior oblique position and a schematic drawing indicating the courses of the major coronary arteries. There is some irregularity of the right coronary artery. The left coronary vessels are small in caliber and show no evidence of atherosclerosis. There is a small amount of catheter-induced aortic insufficiency. Ao. = aorta; Desc. Ao. = descending aorta; RC = right coronary artery; LAD = left anterior descending coronary artery; Circ. = circumflex coronary artery.

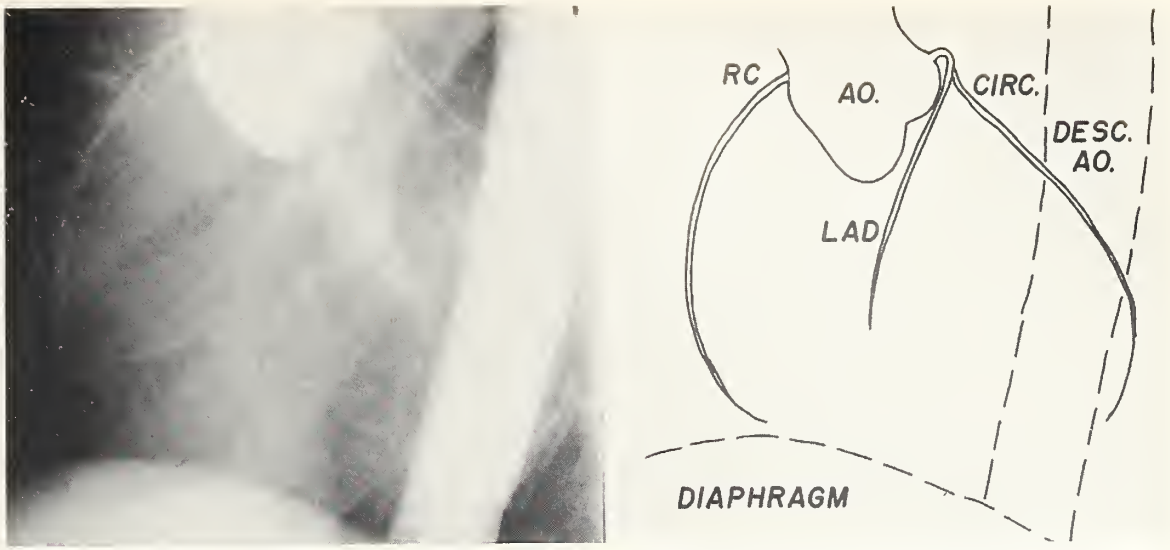


Figure 3.—Coronary arteriogram taken in steep left anterior oblique projection and a schematic drawing indicating the courses of the major coronary arteries. The left circumflex coronary artery is small and descends as a thin marginal artery at the anterior wall of the left ventricle. (Key to abbreviations same as for Figure 2.)

She lost consciousness. The rhythm spontaneously changed to atrial fibrillation with frequent premature ventricular contractions and later reverted to normal sinus rhythm.

Coronary arteriography showed mild, diffuse disease in the right coronary artery; and arising from the left coronary artery was a small circumflex artery which could not be traced more than 2 cm beyond the point of origin. There was a thin marginal artery arising from the circumflex vessel and a small anterior descending artery coming off the left coronary artery (Figures 2 and 3).

In an attempt to prevent ventricular tachycardia, the patient was treated with the beta-blocking agent, propranolol, 60 mg a day. During the next two months she had occasional chest pain but no episodes of unconsciousness. On 9 June 1966 she had another bout of severe chest pain followed by unconsciousness. Propranolol was discontinued and continuous electrocardiographic monitoring was begun. The patient had frequent spells of chest pain and twice had episodes of ventricular asystole (Figure 4) and unconsciousness.

Because of the threat to life inherent in the recurrent ventricular asystole, it was decided to implant an artificial pacemaker, even though the basic rhythm was normal sinus. A transvenous pacemaker was implanted in the right ventricle and the rate was set at 72. As was expected, electrocardiograms showed competition between the artificial pacemaker and the sinoatrial node. After discharge from the hospital the patient had many episodes of chest pain, often of greater intensity than before the pacemaker was implanted. However, unconsciousness did not occur with the pain until October 25, three months after the pacemaker was placed, when the patient had an attack of unremitting, prolonged chest pain and respiratory arrest. With the aid of artificial respiration she was resuscitated and was again put into hospital. The artificial pacemaker was functioning well, but profound, progressive hypotension developed and the

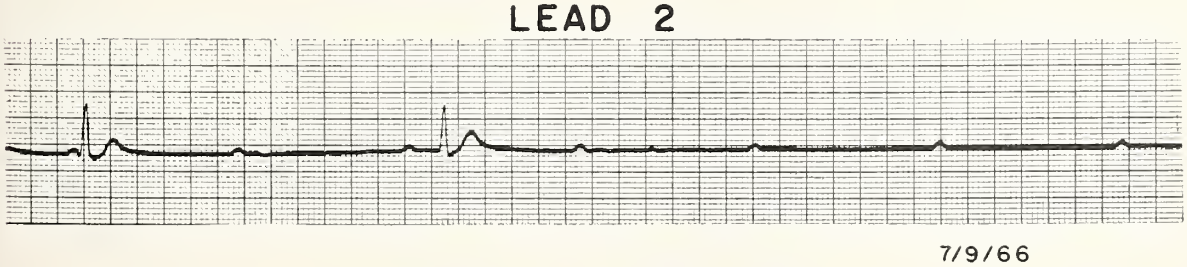


Figure 4.—Electrocardiogram (lead II) taken during an episode of unconsciousness. It shows ventricular asystole for a period of more than five seconds.

patient died. Autopsy showed a mildly atheromatous right coronary artery. The left circumflex artery terminated abruptly 3 cm distal to the bifurcation, descending as a solitary marginal artery at the anterior wall of the left ventricle. The anterior descending branch was small in caliber. There were very small atheromatous plaques lining the left circumflex and anterior descending arteries. These findings were consistent with the coronary arteriogram. Moderate hypertrophy of the left ventricle was noted. There were scattered ill-defined areas of fibrosis in the interventricular septum. The artificial pacemaker was anchored into the apex of the right ventricle. Other significant findings included incipient hilar pulmonary edema, pronounced chronic passive congestion of the liver and congestive splenomegaly.

Discussion

Many of the elements of Prinzmetal's variant of angina pectoris were present in the case here reported. The cyclic nature of the pain and the observations that it was of long standing, was not associated with exercise and that ST elevation was concomitant with it were all typical of Prinzmetal's variant. Abnormalities of rhythm and conduction are characteristic of the syndrome and this patient had, at various times, recurrent ventricular tachycardia, atrial fibrillation, complete heart block with idioventricular rhythm, and recurrent ventricular asystole.

This case was of special interest in two respects. First, there was the correlation of pathological findings with the clinical data. Prinzmetal[3] noted decided narrowing of a major coronary artery in three cases, and he suggested that the variant of angina pectoris was associated with 80 per cent or greater occlusion of one of the three major vessels. The patient described here had only mild atherosclerosis of the right coronary artery. The striking abnormality was the small size of the entire left coronary system, particularly the circumflex artery. Yet the patient had done well for almost 40 years. It would appear that the development of relatively mild coronary atherosclerosis resulted in sufficient impairment of myocardial blood flow to cause angina pectoris and congestive heart failure.

The second point of interest concerned the periods of ventricular asystole which were associated with chest pain. These episodes of cardiac arrest were the reason for implantation of an artificial pacemaker. As was expected, the chest pain was not relieved by this procedure. In fact, the severity of the pain was frequently greater after the operation. It is probable that the artificial pacemaker, by preventing asystole and unconsciousness, provided the basis for the extraordinarily intense pain. In the terminal stage, although the artificial pacemaker functioned well, the myocardium failed and could not sustain life.

Summary

Prinzmetal's variant of angina pectoris was observed in a patient who did not have severe coronary atherosclerosis. The case demonstrated an extremely unusual indication for an artificial pacemaker: Although the patient's basic cardiac rhythm was normal sinus, she was subject to bouts of ventricular asystole in association with angina pectoris, and a pacemaker was implanted for that reason.

REFERENCES

1. Gubbay, E. R.: Prinzmetal's variant angina, Canad. M. A. J., 83:164, 1964.
2. Peretz, D.: Variant angina pectoris of Prinzmetal, Canad. M. A. J., 85:1101, 1961.
3. Prinzmetal, M., Kennamer, R., Merliss, R., Wada, T., and Bor, N.: Variant form of angina pectoris: Preliminary report, Am. J. Med., 27:375, 1959.
4. Robinson, J. S.: Prinzmetal's variant angina pectoris —Report of a case, Am. Heart Jour., 70:797, 1965.

Latent Cerebral Vascular Insufficiency Masked by Long-Term Anticoagulant Drug Therapy

Appearance of Transitory Ischemic Attacks When Drugs Discontinued

JOHN MARTIN ASKEY, M.D., AND JOHN B. DOYLE, SR., M.D., *Los Angeles*

TWELVE YEARS AGO, Millikan, Siekert and Shick[10] reported that anticoagulant drugs stopped characteristic cerebral ischemic attacks in seven patients with intermittent insufficiency of the carotid artery. In a later report they concluded that this therapy was associated with a reduction in subsequent cere-

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bral infarction.[12] Many, if not most, clinicians agree with these conclusions,[4,6,8,9,14] but there are others who disagree.[2,3,11,13]

Further studies on groups of treated versus controlled patients with cerebral ischemic attacks have been considered either inadequately controlled or too small in numbers. Reduction of attacks in the treated groups during treatment and resumption of attacks on withdrawal of the drug has not been regarded as crucially significant. The lack of any practical objective method for measuring the hemodynamic effectiveness of treatment, plus the occasional tendency for repeated attacks to stop spontaneously has led to considerable skepticism.[2,3]

In the presence of such disagreement, all clinical relationships must be carefully studied. Under certain conditions prolonged control studies are not necessary to establish the efficacy of a therapeutic measure.

Hill[5] says that if the results "are dramatic in the light of all past experience," the period of trial need not be prolonged.

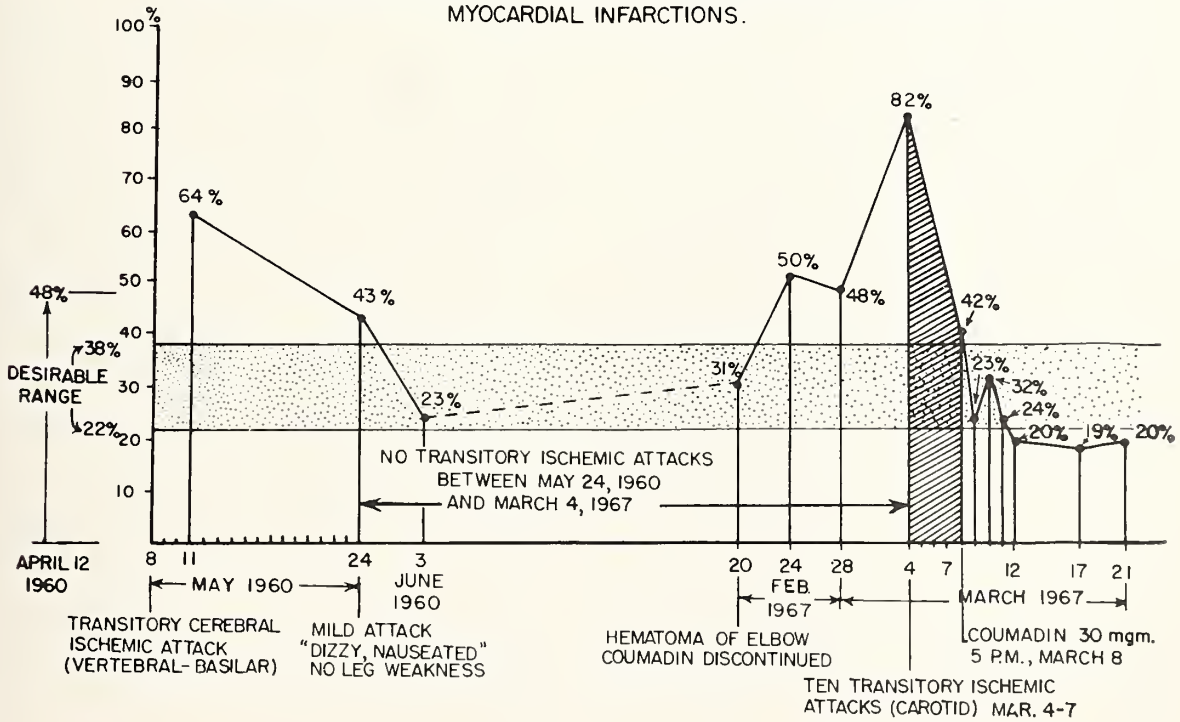
We wish to report the occurrence of transitory ischemic attacks in a patient on two occasions when long-term anticoagulant protection was removed, and the immediate cessation of attacks when anticoagulant control was resumed. On the first occasion the prothrombin level had risen inexplicably to 64 percent (see chart). The second series of attacks occurred more than six years later when warfarin (Coumadin®) therapy was discontinued because of bleeding into the right olecranon bursa. Within two weeks after the discontinuance of the drug, ten attacks of transitory cerebral ischemia occurred over a period of four days. When Coumadin therapy was resumed, the attacks ceased abruptly. In the succeeding five months there were no further attacks.

Report of a Case

The patient, a man, was first seen in 1951 at the age of 54. His weight was 221 pounds and his blood pressure was 164/104 mm of mercury. His mother had died at age 68 of "a stroke" after repeated syncopal attacks. In March 1951 the patient had severe precordial pain and an electrocardiogram tracing was typical of diaphragmatic myocardial infarction. He was given ethyl biscoumacetate (Tromexan®). Later Coumadin was substituted and continued for long-term therapy.

In January 1958 the blood pressure was 172/122 mm of mercury. A month after chlorothiazide

TRANSITORY CEREBRAL ISCHEMIC ATTACKS UNMASKED WHEN PROTHROMBIN LEVELS SUDDENLY ELEVATED. PATIENT ON LONG TERM THERAPY FOLLOWING MYOCARDIAL INFARCTIONS.



(Diuril®) was prescribed it was 144/98 mm. Since then the blood pressure has been controlled except for occasional diastolic pressure measurements over 100 mm. On 8 May 1960, after dinner which included a crab cocktail and a highly seasoned salad, the patient "became dizzy, things went around, my legs felt weak." Thinking that the dinner had caused these symptoms, he took some soda and vomited. In a few minutes he felt all right. Two days later he came to the office. At that time the prothrombin level was 64 per cent. On 24 May he had a mild episode characterized by dizziness and nausea but without weakness of the lower limbs. The prothrombin level was 43 per cent. A neurologist examined him and reported: "The patient suffers from intermittent episodes of basilar artery insufficiency, characterized by vertigo, nausea, nystagmus and weakness of the lower extremities. I should strongly advise his present program of anticoagulation be continued indefinitely." Coumadin therapy was continued.

During the ensuing six years he had few untoward symptoms. He made a trip to Europe and traveled widely throughout this country. On 26 December 1965 he came to the office complaining of a "solid" pain of moderate severity over the lower sternum. An electrocardiogram showed the old evidence of diaphragmatic infarction and also ST-T changes indicative of acute anterolateral myocardial infarction. The prothrombin time was: Control, 14.5 seconds; patient, 27 seconds. Within three months the patient was walking on level places without difficulty.

Following treatment for an episode of acute dyspnea and pulmonary edema on 15 April 1966, he improved rapidly and was soon active and asymptomatic. The use of Coumadin was continued throughout the two attacks of coronary occlusion and the one of acute left ventricular failure. in the course of a routine monthly test on 24 January 1967 the prothrombin times were 15 seconds for the control and 31 seconds for the patient. The dosage of Coumadin was reduced.

On the morning of 20 February 1967 while the patient was walking his dog, his right elbow suddenly swelled until it was the size of a lemon. He was seen at the office where a diagnosis of hematoma of the olecranon bursa was made. At that time the control prothrombin time was 12 seconds, the patient's 18 seconds. Because of the relatively large hematoma, the use of Coumadin was discontinued for the first time in 16 years. Twelve days after the use of Coumadin had been discontinued, his sister-in-law called and said that, while the patient was standing, weakness developed suddenly in the left leg and he had difficulty walking to a chair. When he sat down, he attempted to cross his left leg over his right, but was unable to do so. She said the left side of his mouth drooped and the left side of his face sagged. A few minutes later she called back and said he had totally recovered.

He was admitted to St. Vincent's Hospital where prothrombin time tests indicated the control value to be 14 seconds, the patient's 15 seconds. He was seen by a neurologist who reported: "I saw the patient on March 4 and 5. During the second visit, he had a paretic episode involving the left upper limb and associated with mental confusion. Within a matter of minutes, he had recovered but for slight difficulty elevating the arm to the vertical plane." Two other episodes were observed by a nurse on 5 March. On 6 March the nurse's notes were: "12:45 p.m., difficult to move left forearm. Lasted 3 minutes. 1:05 p.m., confused. Unable to move left hand. 4:00 p.m., awakened confused. Left arm weak, less than 45 minutes, then became normal. 10:30 p.m., weakness in left side. Mental confusion."

When the house physician arrived 10 minutes after the nurse's 10:30 note, the patient was "rational, moving his arm well."

The next day the nurse wrote: "1:00 p.m., confused. Weak arm and leg, lasting a few minutes. 4:00 p.m., confusion and weakness, lasting two minutes."

Thus, in the course of four days, ten transitory cerebral ischemic attacks involving the right internal carotid system had been noted. In the course of consultations with a neurologist and an orthopedist, it was agreed the risk of allowing the episodes of cerebral insufficiency to continue was worse than the risk of further bleeding into the bursa. The orthopedist believed that the hemorrhage was not spontaneous but that the patient had inadvertently bumped or otherwise traumatized the elbow. The arm was bandaged firmly and 30 mg of Coumadin was given. From that time on, the special nurses noted no additional episodes. No further bleeding occurred into the bursa. On the following day the control prothrombin time was 14 seconds, the patient's 20 seconds. On 9 March the prothrombin time was: control, 14 seconds; patient's, 27 seconds. The patient was dis-

charged on 11 March and at the time of last report (August 1967) has had no further episodes.

Discussion

The progressive nature of clinical atherosclerotic disease, with involvement first of the coronary and then the cerebral arteries, was demonstrated in the present case. The appearance of repeated attacks of transitory cerebral ischemia relatively soon after the anticoagulant drug was stopped, and their abrupt cessation when administration was resumed was striking. A similar abrupt cessation of attacks within 48 hours of administration of Tromexin® and dicumarol was described in Millikan, Siekert and Shick's Case No. 1.

The exact mechanism of action of Coumadin or Coumadin-like drugs in relieving transitory ischemia is not clear. The natural history in any one patient is unpredictable. Cerebral ischemia is dependent on the interplay of so many variable factors that the control of a single factor could not be expected to benefit all patients. In Marshall's study of 158 patients with transitory ischemic attacks who had no anticoagulant treatment, 90 (57 per cent) had no cerebral transitory ischemic attacks during the subsequent five years they were observed.[6,7] It was impossible to predict which patients would have infarction. However, three-fourths of those in whom cerebral infarction developed following an ischemic attack in the carotid system, had had only one or two such attacks before the completed stroke. The chief risk of treatment, that of cerebral hemorrhage, occurs mainly in those with hypertension or with already established but unrecognized bleeding, as from an oozing berry aneurysm.[1] In the non-hypertensive patient the risk of cerebral infarction would seem greater than the risk of cerebral hemorrhage.

It is concluded that the possibility of a chance relationship explaining the cessation of attacks following the reinstitution of anticoagulant drug therapy would seem exceedingly remote in the case reported.

Anticoagulant drug therapy, prescribed for coronary artery insufficiency, apparently was of additive although unrecognized value in relieving cerebral artery insufficiency.

Summary

Transitory cerebral ischemic attacks occurred on two occasions in a patient on long-term anticoagulant drug therapy following myocardial infarction. The first attack developed when the Coumadin drug effect was reduced. The apparent protective action of the anticoagulant drug was disclosed when the drug was discontinued because of bleeding. Ten attacks then occurred in four days.

The abrupt cessation of attacks when Coumadin was readministered indicated that an underlying, previously unrecognized cerebral vascular insufficiency had been concealed by anticoagulant drug treatment, and was unmasked when the drug was stopped.

Generic and Trade Names of Drugs

Warfarin—*Coumadin.®*
Ethyl biscoumacetate—*Tromexan.®*
Chlorothiazide—*Diuril.®*

REFERENCES

1. Askey, J. M.: Hemorrhage during long-term anticoagulant drug therapy—Part I. Intracranial hemorrhage, Calif. Med., 106:6-10, Jan. 1966.

2. Baker, R. N.: Discussion in Modern Medicine. Forum—Is long-term anticoagulant therapy indicated for and of benefit to patients with transient episodes of cerebral ischemia? 33:279, 11 Oct. 1965.

3. Fazekas, J. F.: Discussion in Modern Medicine. Forum—Is long-term anticoagulant therapy indicated for and of benefit to patients with transient episodes of cerebral ischemia? 33:276, 11 Oct. 1965.

4. Fisher, C. M.: Discussion *in* Cerebral vascular diseases. Trans. of Fourth Conference of the American Neurological Association and the American Heart Association, Grune & Stratton, Inc., New York, 1965, p. 193.

5. Hill, A. Bradford: Principles of Medical Statistics, Fifth Edition, The Lancet Limited, London, 1950, p. 9.

6. Marshall, J.: Therapeutic agents—Current status *in* Anticoagulant therapy in cerebrovascular disease, Trans. of Fourth Conference of the American Neurological Association and the American Heart Association, Grune & Stratton, Inc., New York, 1965, p. 197.

7. Marshall, J., and Reynolds, E. H.: Withdrawal of anticoagulants from patients with transient ischaemic cerebrovascular attacks, Lancet, 1:5, 2 Jan. 1965.

8. Meyer, J. S.: Discussion, *in* Cerebral vascular diseases, Trans. of Fourth Conference of the American Neurological Association and the American Heart Association, Grune & Stratton, Inc., New York, 1965, p. 197.

9. Millikan, C. H.: Therapeutic agents—Current status *in* Anticoagulant therapy in cerebrovascular disease, Trans. of Fourth Conference of the American Neurological Association and the American Heart Association, Grune & Stratton, Inc., New York, 1965, p. 181.

10. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebrovascular disease: V. The use of anticoagulant drugs in the treatment of intermittent insufficiency of the internal carotid arterial system, Proc. Staff Meeting, Mayo Clinic, 30:578, 1955.

11. Pearce, J. M. S., Gubbay, S. S., and Walton, J. N.: Long-term anticoagulant therapy in transient cerebral ischaemic attacks, Lancet, 1:6, 2 Jan. 1965.

12. Siekert, R .G., Millikan, C. H., and Whisnant, J. P.: Anticoagulant therapy in intermittent cerebrovascular insufficiency, Follow-up data, JAMA, 176:19, 8 Apr. 1961.

13. Van Cleve, R. B.: Letting go of the bear's tail, JAMA, 196:1156, 27 June 1966.

14. Wright, I. S.: Discussion, *in* Cerebral vascular diseases, Trans. of Fourth Conference of the American Neurological Association and the American Heart Association, Grune & Stratton, Inc., New York, 1965, p. 198.

MEDICAL STAFF CONFERENCE

Macroglobulinemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. JOHNSON*: The patient, a 68-year-old white married woman was admitted to hospital because of increasing fatigability. She had been in good health until 1957 when she was found to have enlargment of the spleen. Following radiation therapy the size of the spleen decreased. The patient was asymptomatic until 1965 when she noticed bleeding of the gums, and a hematoma developed spontaneously in the abdominal wall. Seven months before admission to hospital, adminstration of chlorambucil was begun when an increase in lymphocytes and lymphocytoid plasma cells was noted on biopsy of bone marrow. A serum viscosity of greater than 30 units (normal value 1.4 to 1.8 units) and serum protein of 8.8 gm per 100 ml with a large peak at the beta-gamma junction was noted. Plasmaphoresis was performed to decrease serum viscosity.

Two months before admission, peripheral edema developed, for which chlorothiazide was given. The patient continued to feel well until three weeks before admission, when she began to notice easy fatigability and a worsening of edema. Leukopenia was found and chlorambucil was discontinued.

Physical examination. Blood pressure was 125/85 mm of mercury, the pulse rate 78 per minute, respirations 14 per minute and temperature 37C (98.6 F). Physical findings included a flame-shaped hemorrhage in the right fundus and generalized "sausaging" of the veins. The chest was clear to percussion and auscultation. The abdomen was slightly distended, and both fluid wave and shifting dullness were elicited. The edge of the liver was palpated four fingerbreadths below the right costal margin, and the spleen six fingerbreadths below the left costal margin. There was 3+ pitting edema of the ankles and lower legs. Neurological examination demonstrated mild hearing loss bilaterally and mild ataxia of the arms and legs.

Laboratory data. Hemoglobin was 9 gm per 100 ml, packed cell volume 28 per cent, leukocytes 2,000 per cu mm (with the cell differential within normal limits) and platelets 73,000 per cu mm. Serum sodium was 134, potassium 3.8, chloride 103.5, and carbon dioxide 28 mEq per liter. Urinalysis was within normal limits and no protein was present. Creatinine was 0.5 mg per 100 ml, prothrombin time 33 per cent and partial thromboplastin time 100 seconds (normal 55 seconds), alkaline phosphatase 5 Shinowara-Jones-Reinhardt units. Bilirubin was 0.8 mg and serum protein 9.0 gm per 100 ml, with 4.5 gm per 100 ml in a large peak at the beta-gamma junction. Serum viscosity was greater than 40 relative units. No bone marrow examination was done at the time of admission. An x-ray film of the chest showed right pleural effusion. The blood volume was 74 per cent greater than predicted, with a 107 per cent increase in plasma volume and 26 per cent increase of red blood cell volume.

Plasmaphoresis was performed and removal of 14 units of plasma resulted in a fall of serum protein to 7.5 gm per 100 ml with 3.5 gm per 100 ml in the beta-gamma peak. A drop in serum viscosity to 5.7 relative units and a decline in the partial thromboplastin time to 60 per cent, as well as

*Bert Johnson, Intern in Medicine.

a disappearance of the ascites and pleural effusion, were also observed following this therapy.

DR. SCHMID**: Thank you very much, Dr. Johnson. Dr. Malcolm MacKenzie will discuss the pathogenesis of this condition. I hope he will tell us also if this is a specific disease entity, and how to differentiate it from other diseases of protein metabolism.

DR. MACKENZIE*[1]: Thank you Dr. Schmid. This discussion will include an outline of the clinical manifestations of the disorder, comments on the importance of the disease entity, and answers to some of the questions which Dr. Schmid has raised. The information presented is drawn from an analysis of a series of 29 patients whom I have had the privilege of either caring for directly or helped to care for over the past seven years. I will try to examine the underlying disease and its relationship to symptoms in these patients.

Biochemical Considerations

Before we consider the actual disease, I would like to review some biochemical features of this disorder. The gamma globulins of serum are a group of proteins with the slowest electrophoretic mobility by the classic serum electrophoresis technique. These proteins are concerned with antibody formation and therefore are termed immunoglobulins. There are three major classes of immunoglobulins — gamma-G, gamma-A and gamma-M. Two other minor classes of immunoglobulins, termed gamma-D and gamma-E, are trace proteins in serum.

Gamma-G is the principal immunoglobulin in serum, present at a concentration of approximately 1 gm per 100 ml. Gamma-A seems to be the principal immunoglobulin of the digestive tract. It appears in serum at a concentration of approximately 300 mg per 100 ml but it is present also in high concentration in both the salivary and digestive secretions. Gamma-M is the least prevalent in human serum, approximately 100 mg per 100 ml of serum. It achieves importance immunologically, however, because it is the first immunoglobulin to respond to an antigenic stimulus. The proteins included within this group of gamma-M immunoglobulins are familiar as the isoagglutinins of A and B substance in human serum—the Forsmann antibody and the heterophile antibody of infectious mononucleosis.

The basic immunoglobulin molecule is composed of four polypeptide chains, two heavy chains and two light chains. The antibody combining site requires both a heavy and a light chain. Differences between the immunoglobulins reside in the heavy chains—that is, the gamma-G, the gamma-A and the gamma-M all have specific heavy chains which are both immunologically and biochemically unique.

The light chains, in contrast, are similar both immunologically and biochemically in all classes of immunoglobulins. There are at least two major types of light chains, currently called kappa and lambda. The molecules of the immunoglobulins in normal human serum contain roughly 60 per cent kappa molecules and about 40 per cent lambda molecules. In chronic infections a variety of immune competent cells are stimulated and a broad-based gammaglobulin peak is seen on serum electrophoresis; within this gammaglobulin peak, approximately 60 per cent of the molecules will contain kappa chains and 40 per cent will contain lambda chains. This means there will be an elevation of gamma-G kappa, gamma-G lambda, gamma-A kappa, gamma-A lambda, gamma-M kappa and gamma-M lambda.

However, in disorders such as multiple myeloma and macroglobulinemia, only one cell type seems to be stimulated. Therefore only one class of immunoglobulins is stimulated; hence a single narrow peak on serum electrophoresis. The broad based elevation is called a polyclonal gammopathy, and the narrow peak a monoclonal gammopathy.

One further aspect of structure is important. The polypeptide heavy and light chain substructure is held together by disulfide bonds forming a molecule of approximately 160,000 molecular weight. The macroglobulin molecule and some of the gamma-A molecules are composed of a multiplicity of these units; 20 per cent of gamma-A proteins are polymers of two to four such units. The macroglobulin molecule is composed of five units, each with a molecular weight of approximately 200,000. They form then a molecule of 1,000,000 molecular weight. An additional property is the polymerization macroglobulins undergo when they are present in high concentration. In such circumstances they exist in polymers of several million molecular weight. I think this may be important

**Rudi Schmid, M.D., Professor of Medicine.
*[1]Malcolm R. MacKenzie, M.D., Assistant Professor of Medicine.

in the pathogenesis of certain clinical features of this disease entity, particularly the hyperviscosity syndrome.

It is because macroglobulins are immunoglobulins that the interest in this disease is rather extensive. If we could understand how antigen and antibody contribute to a variety of disease states, we would have a much better understanding of the pathophysiology involved. Diseases such as rheumatic fever, glomerulonephritis, Addison's disease, thyroiditis, biliary cirrhosis, pernicious anemia, lupus erythematosus, and rheumatoid arthritis all involve immunological mechanisms.

One approach to this problem is the investigation of the structure of the immunoglobulin molecule. To isolate and obtain pure antibodies in quantities sufficient for definition of structure has been a difficult technical problem. Diseases such as multiple myeloma and macroglobulinemia have achieved prominence because the large amounts of immunoglobulins produced in these diseases can be isolated and studied structurally.

Clinical Features

Macroglobulinemia is a syndrome characterized by a common abnormality — increase in macroglobulins in the serum. I define macroglobulinemia as that disorder in which the gamma macroglobulins in the serum are present in a concentration of 1 gm per 100 ml or greater. This value is ten times the normal value of approximately 100 mg per 100 ml of serum. This definition also encompasses Waldenstrom's definition in which a macroglobulin level greater than 10 per cent of the serum globulins is used as a criterion for diagnosis. It has been said that this is a disorder of elderly men. I question this because in the previously mentioned series of 29 patients there were 16 men and 13 women — hardly a male predominance. The initial complaints of virtually all patients are weakness, fatigue and loss of weight. Symptoms such as mucous membrane bleeding, epistaxis or, rarely, gastrointestinal bleeding are present in 40 per cent of cases. About 25 per cent of the patients complain of some form of neurological abnormality, most often peripheral neuritis. Cerebellar ataxia develops in a small proportion of cases. One patient in the present series became comatose; the symptoms were those of the Bing-Neel syndrome, which can be defined as involvement of the central nervous system in macroglobulinemia. Frequent infection is not a common concomitant of macroglobulinemia. Of the 29 patients only one sought medical attention for this problem. This is important because in multiple myeloma recurrent infection is a common reason for the patient's seeing a physician.

Often the condition comes to light in the course of routine laboratory studies done in preparation for elective surgical operation, anemia being the most common abnormal finding. In fact 24 of the 29 patients in the series under discussion were anemic at the outset of the illness.

Useful physical findings in this disease are limited. Lymphadenopathy (usually microadenopathy) occurs in about one-third of cases. Patients who had significant adenopathy usually had a more aggressive form of the disease. Hepatomegaly was found in 68 per cent of the patients, a higher proportion than has been reported in the literature. (The usual figure given is 40 per cent.[2-5]) In the series splenomegaly was present in 35 per cent of the patients I observed, and hepatosplenomegaly in the same proportion. The signs of hyperviscosity occurred in 40 per cent of the patients.

It has been suggested that the absence of osteolytic lesions as observed roentgenographically in these patients is a useful differential point between myeloma and macro globulinemia. This is not the case. In three patients osteolytic lesions developed during the course of illness. All three have had lymphosarcomatous infiltration, not plasmocytic infiltration, in pathological specimens.

Laboratory Findings

Anemia is very prominent in these patients. It usually is normochromic, normocytic anemia, although some patients, particularly those who have had bleeding phenomena, will have an additional component of iron deficiency. The leukocyte count and the cell differential are usually within normal limits. Lymphocytosis is said to be frequent, but it was present in only two of the 29 patients I observed, both of whom were thought to have chronic lymphocytic leukemia or leukolymphosarcoma with abnormal peripheral lymphocytes. Bence Jones protein was present in the urine in 10 per cent of the patients and one of the patients with lytic lesions in bone also had Bence Jones proteinuria. Hence, differential diagnosis becomes quite important. The Sia water test was positive in 50 per cent of patients. (The incidence of positive reaction to this test reported in the literature is

80 per cent.) The Sia test is a water dilution test for euglobulins. It is extremely simple and is useful as a screening test. If the result is positive—and by positive I mean a large amount of flocculent curdy precipitate—then one is alerted to a diagnosis of macroglobulinemia. All of these patients have had a narrow-based peak on serum electrophoresis. The mobility of the peak is not helpful. It has been said that a fast gamma peak suggests macroglobulinemia. This is not true. In several cases there were very slow gamma peaks. The level of total protein is useful though not diagnostic, as in today's patient—8.8 gm of total globulin per 100 ml. Most patients have only a mild elevation of gamma globulins and it is uncommon to have as much as 14 or 15 gm per 100 ml. Such elevations are more likely to be present in multiple myeloma.

Immunoelectrophoresis is mandatory to define any pronounced symmetrical elevation of gamma globulin. Elevation of this type may represent a myeloma protein (gamma-G or gamma-A) which may not make a therapeutic difference. But if it is a gamma-M and, thus, macroglobulinemia, this differentiation does have therapeutic significance. In three cases in this series the diagnosis was changed from myeloma to macroglobulinemia on the strength of the result of this test. In our patients the test used most frequently is determination of the relative serum viscosity. We find this is a very useful tool, particularly for gauging the progress of patients and for decisions about therapy.

Bone marrow examination in these patients is complex. In Figure 1 three forms of cells can be seen—plasma cells, classical lymphocytes and interesting intermediate cells which have been called lymphocytoid plasma cells or plasmacytoid lymphocytes. In the bone marrow from any given person, one may see fields with all three cell types or fields with only plasma cells, or only lymphocytes. Unless the bone marrow is examined carefully an erroneous diagnosis of myeloma may be made because of the occasional predominance of plasmacytes. The lymphocytoid plasma cells are often found in the organs of these patients. Infiltration of the lymph nodes, the spleen and the portal areas of the liver (but not the parenchyma) is common. I have come to regard hepatic parenchymal infiltration as prognostically ominous. Extensive infiltration into the kidneys is very common and has no prognostic significance. There are few defects of renal function in patients with macroglobulinemia. Defects of acidification have been described but actual renal failure in this disorder is quite uncommon.

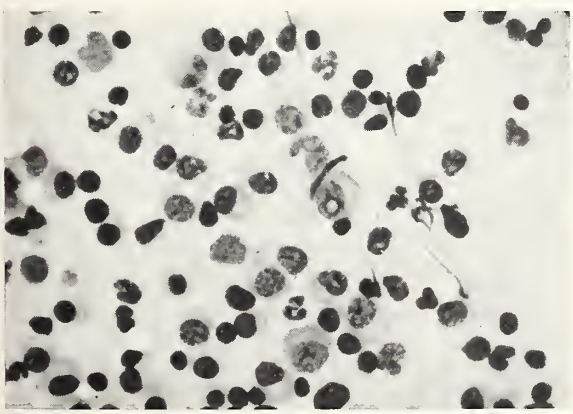


Figure 1.—Bone marrow smear from patient with macroglobulinemia demonstrating plasma cells, lymphocytes and intermediate cell forms (×160).

The Hyperviscosity Syndrome

Serum viscosity is very important because the severity of this disorder is variable and treatment must be individualized. Some patients with this syndrome will survive for many years without symptoms. Conversely, other patients will have an extremely malignant course resembling that seen in lymphosarcoma.

In determining plasma or serum relative viscosity, an Oswald capillary viscometer is used. Five milliliters of serum is placed in the reservoir and passed through the capillary by gravitational force. Saline solution or water is used as a control. The time it takes the serum and the control solution to pass through the capillary is measured. The time for the serum is divided by the time for the control. This value is expressed in relative units. Normal serum gives a value of approximately 1.4 to 1.8. In macroglobulinemia it is usually increased.

Any elevation of serum proteins will result in some increase in serum viscosity. Chart 1 demonstrates a plot of the concentration of protein in gm increments against relative viscosity. With elevations of gamma-G the viscosity usually does not rise above 2 or 3. In many cases of macroglobulinemia a rise in protein concentration leads to a rapid increase in viscosity. Not all macroglobulins or gamma-G proteins behave this way, but it is a useful generalization.

Patients with increased serum viscosity have characteristic clinical manifestations. Symptoms of

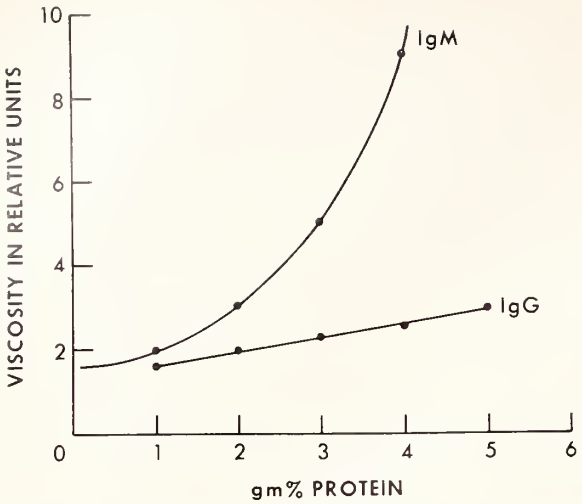


Chart 1.—Plot of serum protein concentration against relative viscosity. IgM = gamma M globulins, IgG = gamma G globulins.

hyperviscosity include fatigue and weakness, excessive bleeding (particularly epistaxis, bleeding gums, rectal bleeding and menorrhagia), ocular symptoms such as blurring of vision, or even loss of vision, neurological symptoms such as hearing loss, vertigo and coma, and finally death. Specific physical findings are limited to the fundus where retinal hemorrhage, dilated and distended "sausage" veins are seen (Figure 2). One of the problems encountered is that each patient seems to have his own individual threshold for the appearance of symptoms. Most patients will have symptoms at a relative viscosity level of 8. In some patients, however, symptoms have developed below that level. For example, one patient became "fatigued" when serum viscosity reached 6, and had cardiac failure when it rose to 8. Another had retinopathy at a viscosity level of 8, bleeding at 10 and nystagmus and vertigo at 20. The patient presented today had severe hyperviscosity with minimal symptoms. When she entered the hospital serum viscosity was 40 and she had mild hearing loss and minimal cerebellar ataxia. In most patients death would come before such a level was reached.

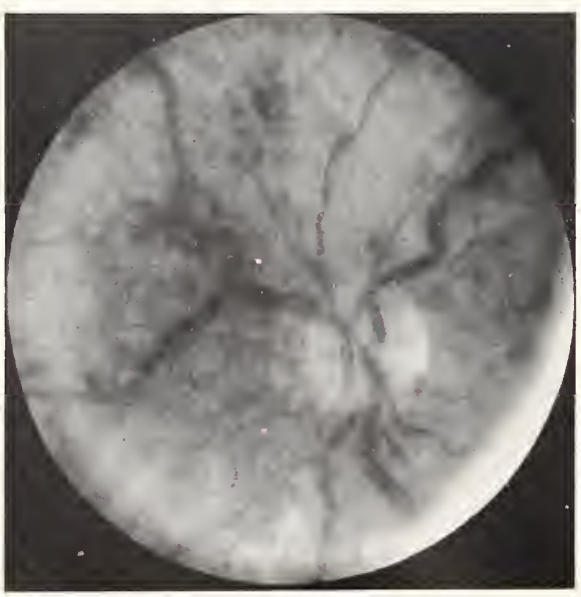


Figure 2.—Photograph of fundus from a patient with macroglobulinemia demonstrating the characteristic "sausaging" of the retinal veins.

Abnormalities in blood volume occur frequently in patients with this disorder. In such instances a comparison of relative viscosity with total blood volume demonstrates a rough correlation between these two factors. In examining this further, one finds that many of the patients do not have any abnormalities of red cell mass and most have only a mild decrease. Some patients have a very low red cell mass, but in them the course of disease tends to be more malignant. The red cell mass then does not contribute to the increase in blood volume.

A comparison of deviations in plasma volume with relative viscosity divides the patients into two groups. At a level of 4 relative units, most patients will be asymptomatic and have only a modest elevation of plasma volume. However, patients with high relative viscosity will have a very large plasma volume. The plasma volume in the patient presented today was increased 107 per cent. These changes are under etiologic investigation. In general, these patients are not edematous, but today's patient had both edema and ascites, and for a long time I had suspicion that she had infiltrative disease in the liver. I am still not sure that she does not.

The cause of the anemia in these patients is very complex. Dr. Martin Cline made a study of this problem and concluded that the anemia was due to relative bone marrow failure — that is, the bone marrow does not keep up with the loss of red cells in the periphery. There may be also a component of iron deficiency, particularly in patients with bleeding problems. Clearly an additional factor is the elevated plasma volume.

Treatment

Common therapeutic measures include observation, the administration of alkylating agents and prednisone, and plasmaphoresis. Alkylating agents

have been strongly advocated by other observers. In my own experience only about 30 per cent of patients have responded to them. Perhaps these are biased data, influenced by the fact that patients with more severe forms of the disease are referred here. At the same time, alkylating agents can be dangerous, particularly in patients who do not need them. Patients with the hyperviscosity syndrome are usually treated with plasmaphoresis. Patients who can be kept free of symptoms with plasmaphoresis no more than twice a month are treated with this method only. If more vigorous therapy is required, then alkylating agents are usually used. In the patient with mild disease and no evidence of hyperviscosity, observation is the treatment of choice.

To summarize, macroglobulinemia is a syndrome with a broad spectrum of clinical manifestations. Decision as to how to treat patients with this disorder is based entirely upon the clinical symptoms. In general one should be conservative rather than vigorous.

DR. SCHMID: Dr. MacKenzie, some years ago, Bloch and, I think, Levin in Texas, suggested that one could treat these patients with penicillamine to break disulfide bonds which unite the macroglobulin molecules. Would that change viscosity and improve symptoms?

DR. MACKENZIE: Penicillamine was tried and it worked fine in the test tube, but it does not work well in the patient. Why it is ineffective is uncertain. It is true that if these molecules are split, the serum viscosity will decrease. To date, this has not proved to be a very fruitful therapeutic approach.

EDITOR'S FOLLOW-UP:

Following discharge from hospital the patient again noted weakness and easy fatigability, and serum viscosity was found to be elevated to 40 units. She was readmitted on two occasions, plasmaphoresis was performed both times and the symptoms improved and serum viscosity decreased toward normal. Because of the difficulty in controlling the symptoms, both chlorambucil and prednisone were tried, without obvious benefit. These drugs have been discontinued and she is currently free of symptoms. Should hyperviscosity recur, plasmaphoresis will be used to control symptoms.

REFERENCES

1. Barth, W. F., Wochner, R. D., Waldmann, T. A., and Fahey, J. L.: The metabolism of human gamma macroglobulins, J. Clin. Invest., 43:1036, 1964.

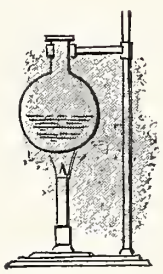
2. Cohen, R., Bohannon, R., and Wallerstein, R.: Waldenstrom's macroglobulinemia. A study of ten cases, Amer. J. Med., 41:274, 1966.

3. Dutcher, T. F., and Fahey, J.: The histopathology of the macroglobulinemia of Waldenstrom, J. Nat. Cancer Inst., 22:887, 1959.

4. Imhoff, J., Baars, H., and Verloop, M.: Clinical and hematological aspects of macroglobulinemia of Waldenstrom, Acta Med. Scand., 163:349, 1959.

5. Martin, N.: Macroglobulinemia, Quart. J. Med., 29: 179, 1960.

6. Schwab, P., and Fahey, J.: Treatment of Waldenstrom's macroglobulinemia by plasmaphoresis, New Eng. J. Med., 263:574, 1960.



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EDITORIAL

Two Centennials

THIS MONTH and next month the two oldest county medical societies in California celebrate the one hundredth anniversary of their birth. Each claims uninterrupted continuity since 1868 and each gently challenges the other's presumption of primacy. San Francisco's evidence that it was founded in February of 1868 hangs by a slender but apparently continuous thread. The thread is the "Cash Book" for the Society which was opened in February 1868, meticulously kept and somehow survived the fire of 1906 to serve a few more years. All of the Society's other records were destroyed. Sacramento claims March of 1868 as the month of its birth, and so far as we know its continuity since that time has not been seriously disputed.

The San Francisco Medical Society and the Sacramento Society for Medical Improvement are both to be congratulated upon a first century of vigorous achievement. Elsewhere in this issue Mary Mathes recreates something of the atmosphere of those early days and writes entertainingly of medical science, doctor-patient relationships and even socioeconomics as viewed by physicians a hundred years ago in California. Much of this was very different from what exists now, while some of the unresolved problems she discusses have an all too familiar ring even after a century of truly unprecedented progress.

While San Francisco may claim to have got there "fustest" and even to have been recognized first in this issue of CALIFORNIA MEDICINE, Sacramento will come in next month with the "mostest" since much of the March issue will be devoted to commemorating the Centennial of the Sacramento Society for Medical Improvement.

No doubt the question of which Society was founded first will continue in debate, and will therefore continue to stimulate further scholarship to fascinate us all concerning this early and turbulent period of medicine's history. CALIFORNIA MEDICINE salutes both these distinguished medical societies and wishes them well as they enter a second century of vigorous service to their members, the profession as a whole and the people of the county and the state.

Lester Breslow

THE RESIGNATION of Dr. Lester Breslow as Director of The California State Department of Public Health terminates a career of more than 20 years in the state health department. During this period Dr. Breslow had many contacts among practicing physicians throughout the state and earned the respect of those who worked with him. In the two years he was director of the Department he continued a long tradition of liaison and dialogue between the Department and the California Medical Association, which over the years has resulted in a degree of cooperation between private practice and public health in California that is almost unique in the nation.

Dr. Breslow has been a regular contributor of authoritative and informative communications on public health to CALIFORNIA MEDICINE. He was active in the formulation of the Medi-Cal program and has staunchly supported the mainstream concept of medical care. He has been an indefatigable foe of undiscovered phenylketonuria, of preventible measles, of the evils of cigarettes and smog and, most recently, of unnecessary noise.

Dr. Breslow has chosen to extend the reaches of his career by accepting a professorship in Health Service Administration at the School of Public Health, University of California, Los Angeles, at the very moment he is at the pinnacle of recognition by his peers. He will be the next president of the American Public Health Association.

It is good that this knowledgable and always stimulating physician will remain in California.

Peritoneal Dialysis in Chronic Uremia

THE POOR RESULTS with long-term peritoneal dialysis reported elsewhere in this Journal agree with the experience of most other renal centers. In those virtually anephric patients who survive for longer than three or four months on peritoneal dialysis, progressive malnutrition, osteodystrophy and crippling neuropathy become an increasing likelihood. As chronic hemodialysis and homotransplantation are clearly more effective modes of therapy for end-stage renal failure, chronic peritoneal dialysis has been virtually abandoned at major renal centers. To avoid trapping patients into an intolerable existence, even further attempts at "exploration and refinement" of chronic peritoneal dialysis should be carried out only if the option to switch to more effective and less traumatic therapy is readily available at short notice.

Nevertheless, in many circumstances peritoneal dialysis is an invaluable tool in the handling of patients with chronic uremia. Acute decompensation in a previously stable, moderately azotemic patient may be due to reversible causes. The safest therapy for such patients, as is pointed out by Edelbaum and coworkers, may be dialysis. In those circumstances peritoneal dialysis, which can be satisfactorily performed by those skilled in its use, has great merit. During and after control of dangerous uremic complications in such patients, renal function may be improved by treatment of congestive failure, infection, volume depletion, uncontrolled hypertension or intercurrent acute tubular necrosis. A common fear, which restrains the general physician from utilizing peritoneal dialysis in such cases, is that once the patient is begun on dialysis he will immediately need chronic dialysis. The frequency of backing inadvertently into chronic peritoneal dialysis (pending a decision on hemodialysis or transplantation) can be sharply reduced by a clearer understanding by both physician and patient of the natural history of chronic renal failure. In advanced chronic renal failure, the transition from asymptomatic, chemically severe azotemia to severely symptomatic uremia may occur very rapidly and without visible cause. Only if the physician requires and the patient enables close follow-up and therapy (at progressively shorter intervals of time) will it be possible to distinguish reversible deterioration in renal function from the natural ending of renal disease.

Likewise, it must be appreciated that the phase of rapid "idiopathic" deterioration occurs at widely differing levels of serum creatinine and urea from patient to patient. Finally, indavertent, chronic peritoneal dialysis can be avoided by early referral of patients to major renal centers for a decision regarding suitability of the patient for eventual chronic hemodialysis or transplantation. As the patient approaches the phase of transition from asymptomatic, chemically severe azotemia to severe, symptomatic uremia, the major renal center can embark on definitive therapy. The only limiting factor in this orderly scheme, at present, is the serious lack of funds, facilities and trained personnel to carry out definitive therapy of chronic uremia.

Exfoliative Cytology in Gastric Cancer

SUCCESSFUL CYTOLOGICAL study of the stomach requires fulfillment of several critical conditions. The most important is that cell collection, processing and scanning be performed by trained cytotechnologists. The stomach must be clean and the patient adequately hydrated to assure recovery of enough lavage fluid for processing. In patients with stomach obstruction, careful cleansing with a large-lumen Ewald tube, and occasionally overnight gastric suction, is required before the examination. The final diagnosis must be made by an *interested* and skilled pathologist or clinician.

The pathologist should select from among only three terms in reporting on gastric exfoliative cytology specimens: benign, malignant or unsatisfactory. The unsatisfactory examinations should be repeated. Diagnostic reports such as "Class I"

(or Classes II, III, IV or V) or "suspicious," "doubtful," "atypical," "highly atypical" should be abandoned, since they reflect insecurity with cytological interpretation and serve only to confuse the clinician caring for the patient. If he had not been suspicious or doubtful, it is unlikely that he would have referred the patient for cytological examination. Furthermore, a surgical operation is the early legacy for most patients in whom a diagnosis of this kind is made. At operation the majority of these patients are revealed to have alterations in benign cells due to peptic ulcer, to metabolic abnormalities such as Vitamin B_{12} or folic acid deficiency, to atrophy or "gastritis,"—conditions that usually can be managed conservatively. By insisting on an interpretation of either benign or malignant, the responsible physician can substantially increase his accuracy.[3]

Elsewhere in this issue of CALIFORNIA MEDICINE, Kernen and Bales have demonstrated a laudable accuracy in gastric cytological examination with full recognition of the difficulties and the limitations of this laboratory technique. They have made a significant contribution to accurate diagnosis in the patients under consideration. Although their series is small, their data are similar to those reported from other centers utilizing lavage with saline solution for cell collection.

The only exception is Schade's[5] report of only 2 per cent false negatives in 282 cases of gastric cancer and 5 per cent false positive results in 276 patients with benign disease. This report is difficult to interpret, since Schade discussed only the patients upon whom operation was subsequently performed. The total number examined was 2,443, leaving 1,885 unaccounted for in ultimate diagnosis. In another report from this group[4] an unequivocal diagnosis of "malignant" was made in 64 per cent of 115 patients with gastric cancer, and in an additional 20 per cent the specimens were considered to be "highly atypical." The latter were considered to be correct for cancer, making a total of 84 per cent positive. In a group of 37 patients without cancer (the total number examined was not reported) an erroneous diagnosis of malignant disease was made in five. In three other patients cells "suggestive of malignancy" were observed, and in the remaining 29 patients "highly atypical" cells were observed. The "highly atypical" cells were considered to be benign in these patients.

The best reported data on gastric exfoliative cytologic examination have resulted from utilization of alpha-chymotrypsin in an acetic acid-acetate buffer at pH 5.6 as the lavage fluid.[1-3] Review of coded slides[1] without foreknowledge of collection techniques, clearly demonstrated that chymotrypsin specimens were superior in morphological preservation and in numbers of malignant cells and in allowing for correct diagnosis. These comparisons were made with specimens collected by vigorous lavage with normal saline or Ringer's solution, by abrasive techniques or by aspiration of the fasting gastric contents.

Although Kernen and Bales report accuracy which is in the same order of magnitude as that achieved by others utilizing saline solution lavage, it would seem that the additional 10 to 14 per cent increase (93 to 97 per cent) in accuracy obtainable by chymotrypsin lavage in cancer patients would be worth exploring. The method is as simple as lavage with saline solution, and the specimen appears to be superior for diagnostic purposes. The false positive rate reported by Kernen and Bales is of the same order as that of the chymotrypsin series[1-3] and demonstrates the accuracy that can be achieved in benign disease by careful interpretation.

The major role of expert gastric cytologic examination in the United States is in the precise diagnosis of lesions that have been demonstrated by roentgenographic or gastroscopic examination or have been clinically suspected without such demonstration. As the most sensitive diagnostic technique for cancer involving the stomach, it is also useful in demonstration of recurrence of malignant growth. Its most important contribution to patient welfare may be the exclusion of the diagnosis of malignant disease. Correct cytological interpretation will almost invariably provide a correct tissue diagnosis before operation. It is useful to the surgeon to know whether there is an adenocarcinoma or a malignant lymphoma of the stomach. For example, approximately one-half of cures in gastric cancer occur in malignant lymphoma (resection plus postoperative irradiation therapy) although these lesions make up only 2 to 3 per cent of malignant lesions of the stomach.

In the past 30 years the cure rate of gastric carcinoma by surgical operation has increased, if at all, only from 7 per cent to 8 per cent of all patients. (It must be borne in mind, however, that

improvement in preoperative care and preparation, safe blood transfusion and expert postoperative care have made it possible to operate upon a higher proportion of patients.) Much more encouraging has been the progressive decline in the incidence of gastric carcinoma in the United States during this period. Surgical therapy should still be attempted in all patients unless there is strong medical contraindication or distant metastatic lesions are evident. Gastric cytologic examination aids in the decision for or against operation.

It is to be hoped that reports such as that of Kernen and Bales will stimulate wider application of this valuable diagnostic method. Physicians disenchanted with gastric cytologic examination have probably been denied the diagnostic aid available from expert use of the method, as described in this paper.

REFERENCES

1. Brandborg, L. L., Taniguchi, L., and Rubin, C. E.: Is exfoliative cytology practical for more general use in the diagnosis of gastic cancer?—A simplified chymotrypsin technique, Cancer, 14:1074-1080, 1961.

2. Brandborg, L. L., McDonald, W. C., Rubin, C. E., and Gottlieb, S.: Cytological diagnosis of gastric cancer by chymotrypsin lavage, Recent Advances in Gastroenterology I:300-307, Third World Congress of Gastroenterology, Tokyo, 1967.

3. MacDonald, W. C., Brandborg, L. L., Taniguchi, L., and Rubin, C. E.: Gastric exfoliative cytology: An accurate and practical diagnostic procedure, Lancet, II:83-86, 1963.

4. Reece, M. F., Boon, T. H., and Schade, R. O. K.: Exfoliative gastric cytology. Its evaluation in the diagnosis of carcinoma of the stomach, Lancet, II:1163-1164, 1961.

5. Schade, R. O. K.: Gastric cytology: Principles, methods and results, Edward Arnold (Publishers), Ltd., London, 1960.

The Scope of Medicine

MODERN ADVANCES in medical science are beginning to pose important moral, ethical and social questions as these new developments become applicable or are actually applied in practice. Elsewhere in this issue, Rubini and Goldman consider some of the sociological aspects of dialysis and renal transplantation. As this is written, dramatic attempts to transplant human hearts are being made on two continents and interest in the social implications of these scientific developments is rapidly becoming more widespread. The role of the physician and of the medical profession with respect to issues such as these has not been adequately discussed or clearly defined. There are many differing views both within the profession and elsewhere concerning the true scope of the responsibility of modern medicine to modern society in a rapidly changing scientific and social environment.

Should the responsibility of the physician be simply to save life, relieve suffering and restore function in his fellow human beings? Few today would say that the scope of medicine does not extend far beyond this. But how far and in what directions? Prevention of illness, injury and emotional disturbance; rehabilitation of those who become afflicted, and something called health maintenance for those who are well are surely within the purview of the physician. Does this purview, however, extend to well-being of the person as a whole and to his adjustment with his physical and social environment?

In passing, it is noteworthy that the World Health Organization has defined health as a "state of complete physical, mental and social well-being and not merely the absence of disease."

If all this is true and accepted, then the characteristics of the physical and social environment logically also come within the scope of medicine and the purview of the physician.

But the scope of medicine may even extend far beyond this. Recent advances in science clearly foreshadow a capability to tamper with the fundamental biology of the species and thus profoundly to influence human evolution within the framework of an ever changing scientific and social environment. All of this is awesome but it is upon us. Medicine surely has some knowledge and experience to bring to bear upon the moral, ethical and social questions which must now and henceforth find practical and realistic answers.

To date there has been surprisingly little dialogue concerning what should be the true scope of medicine with respect to these problems in modern society. The editors of this journal believe there should be more discussion of this important subject, and would consider providing a forum for an exchange of thoughtful, constructive and concisely formulated views, were such to be forthcoming from among its readers.

California Medical Association

Council Highlights

Highlights of the Actions of the California Medical Association Council Meetings, 4 November and 9 December 1967

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA Headquarters office.

538th Meeting, 4 November, San Francisco

Medi-Cal again Occupied the Center Ring at the November CMA Council meeting in San Francisco. After applauding director of Health Care Services Carel Mulder (who said his office believes in and places emphasis on the importance of peer judgment as a control in the Medi-Cal program, and who attempted to "set the record straight" in regard to how the adverse publicity resulting from the "1200 situation" developed), the Council adopted a 12-point policy statement, which reaffirmed CMA's desire to provide Medi-Cal recipients with the same needed high quality health care as is available to the public at large and urged that Medi-Cal be restored to the comprehensive dimension it had prior to 1 September 1967, as contained in Assembly Bill 5.

The Council also approved a statement which said: "The California Medical Association deplores recent reported and factually inaccurate statements which tend to suggest abuse of the Medi-Cal program by members of our profession. Full cooperation by the State Administration in correcting such misinformation is needed to obtain maximum support of the Medi-Cal program by individual physicians throughout the state."

A Report by the Committee on Organizational Review and Planning recommended concurrent officer elections for county societies; new, improved ways of communications between CMA and component societies; more debate in open Council sessions; more representations by component societies to the Council, and continued regional meetings of society presidents as a supplement to the annual County Society Officers Conference.

The Council Bade Farewell to AMA President-Elect Dwight L. Wilbur, who was attending his last meeting of CMA Council as a member. In his farewell remarks, Doctor Wilbur paid tribute to

JOHN G. MORRISON, M.D. President
MALCOLM C. TODD, M.D. President-Elect
WILLIAM F. QUINN, M.D. Speaker
JOSEPH F. BOYLE, M.D. Vice-Speaker
ALBERT G. MILLER, M.D. Chairman of the Council
HAROLD KAY, M.D. Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D. Secretary
MALCOLM S. M. WATTS, M.D. Editor
ROBERT L. THOMAS Executive Director
General Office, 693 Sutter St., San Francisco 94102 • 415 776-9400
JACK CURLEY Southern California Office
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RICHARD W. LEMOS Sacramento Office
1127 11th St., Sacramento 95814 • 916 444-7496

the Council and to those with whom he has worked for the past 20 years as editor of CALIFORNIA MEDICINE: the editorial board, Howard Hassard, Robert Thomas, John Hunton, Robert Edwards and Barbara Rooney. He offered this advice*: 1) The Council must maintain unity of purpose, even though the approaches or means of various councilors may differ; 2) The basic goal of the Council must be to maintain the free practice of medicine, with the voluntary association of the patient and physician as the measure of this freedom, and 3) The patient must always be thought of as a person.

Councilor Malcolm S. M. Watts, who will soon assume the position of Editor of CALIFORNIA MEDICINE, expressed his thanks to the Council for the confidence and trust placed in him. [Dr. Watts became Editor 1 January 1968.]

A Resolution Adopted by the San Francisco Medical Society reminding all physicians of their obligation to adhere to the "usual, reasonable and prevailing" concept when dealing with Medi-Cal patients, and calling on utilization review committees to intensify their efforts to identify abusers of the program, was approved by the Council.

A Committee on Emergency Medical Care was established and charged to conduct a survey of emergency rooms in California Hospitals.

Chairman of the Commission on Hospital Affairs James MacLaggan reported to the Council that the ad hoc Committee on Standardization of Medical Records met with representatives of the Nurses' Association, California Hospital Association and Medical Record Librarians, and are giving further consideration to the problem.

The Council Approved a Recommendation Made by the President of the Woman's Auxiliary to the Tulare County Medical Society, whereby a pilot project would be conducted to attract physicians to rural areas.

539th Meeting, 9 December, Los Angeles

Two New Blue Shield Group Health Prepayment Plans for physicians, their families and employees that will cover both hospitalization and physicians' services were approved by the Council at its December meeting. Information about the new plans will be distributed to the membership as soon as it is available.

Highlights of the New Report on Professional Liability in California by the Division of Socio-Economics and Research were discussed, and the Council voted to make it available to anyone who requests a complete copy. The information also will be used to deveolp a *Socio-Economic Report* in the near future.

*The full text of Dr. Wilbur's remarks was printed on page 71 of the January issue of CALIFORNIA MEDICINE.

New Chairman of the Scientific Board will be Dean Charles John Tupper of U.C. Davis School of Medicine. He will assume chairmanship after the 1968 Annual Session. The Council also accepted the Scientific Board's proposals for 1) creation of a Committee on Accreditation for postgraduate education programs; 2) establishment of a committee on continuing education in each California hospital by its medical staff; 3) distribution of money (allotted to the board by CMERF) to medical schools with active departments of continuing medical education, and 4) restricting new scientific sections to those specialties that have primary American boards. In addition, a recommendation for increased support of the educational activities of the Committee on Cancer was referred to the Finance Committee, and House of Delegates resolutions on "nurse midwifery" and "the assistant physician" were referred to an ad hoc study group that will include representatives of the California Hospital Association and the California Nurses' Association.

The Committee on Legislation reported that CMA-sponsored legislation next year probably will include a bill to legally define death; the Scientific Board is working on this piece of legislation. Another bill that would allow physicians to treat minors (especially teenagers) without parental consent also will be sponsored by the CMA.

The Report of the National Commission on Health Manpower was referred to the Committee on Organizational Review and Planning for study.

The California Coordinating Committee for Regional Medical Programs has received at least 17 grant applications. Programs proposed in the applications included some for coronary care unit training; communications and information programs; a program for stroke case finding, and a postgraduate school for physicians practicing in the Watts area of Los Angeles. A special meeting of the CCCRMP board will be held to consider which applications should be approved for transmittal to Washington.

An Ad Hoc Committee on Constitution and Bylaws, whose function would be to assist in updating and revising these documents, was announced. The Committee is composed as follows: James C. MacLaggan, M.D., Chairman; Roberta F. Fenlon, M.D.; Homer C. Pheasant, M.D.; Wilbur G. Rogers, M.D., and Robert L. Watson, Jr., M.D.

State Implementation of Public Law 89-749, Doctor Malcolm Todd stated that the California Health Planning Council (of which he is an appointed member) had had six meetings and had established criteria for local participation in the program. Doctor Todd commended the program being developed in San Diego County. He stated that a brief, explanatory pamphlet on Public Law 89-749 is currently being prepared by the CMA

Task Force on 89-749. When completed, the pamphlet will be distributed to the membership.

The Following Committee Appointments Were Made:

Medical Staff Survey Committee—John B. Dillon, M.D., Los Angeles.

State Department of Public Health Advisory Committee on Indian Health—Stanley A. Skillicorn, M.D., San Jose.

Committee on Emergency Medical Services—Carl E. Anderson, M.D., Santa Rosa, Chairman; William L. Argo, M.D., Fresno; Eugene M. Webb, M.D., San Francisco; Thomas W. Lyons, M.D., La Mesa; Thomas Rossitto, M.D., Auburn; Charles C. Henderson, M.D., San Mateo; Phillips Dunford, Jr., M.D., Bakersfield; Edward Blasdel, M.D., Berkeley, and Wayne P. Chesbro, M.D., Berkeley, Consultant.

Legislative Committee — Tirso Del Junco, M.D., Los Angeles (replacing John Rumsey, M.D., San Diego, resigned).

Committee on Alcoholism — Nicholas Khoury, M.D., Los Angeles, Chairman; Alfred Auerback, M.D., San Francisco; R. S. Hockwald, M.D., San Francisco, and, as Consultants, John R. Philp, M.D., Santa Ana, and A. C. Hollister, M.D., Berkeley.

Committee on Other Professions—Warren L. Bostick, M.D., Irvine (replacing Wayne Pollock, M.D., deceased).

Committee on Welfare Medical Care Programs—Richard D. Miller, M.D., Los Angeles.

Organizational Review and Planning — Stanley Moore, M.D., San Diego (replacing Robert Hood, M.D., Van Nuys, resigned); Robert C. Combs, M.D., Irvine.

Committee on Voluntary Health Agencies—Lewis T. Bullock, M.D., Los Angeles.

Committee on Continuing Medical Education, Area Representative — Woodbury Perkins, M.D., San Diego.

Doctor Eugene F. Hoffman, Sr., Chairman of the CMA Delegation to the AMA, presented some highlights of the Clinical Convention of the AMA in Houston. He stated that the CMA Delegation was actively involved in every phase in which important decisions were made in the interests of the public and the medical profession. Five of the 57 resolutions considered by the AMA House were introduced by California. The House adopted Resolution No. 37 (bringing the 1973 Clinical Convention to Anaheim, rather than Las Vegas) and referred to the Board of Trustees the remaining four California resolutions. Doctor Hoffman also reported that five members of the delegation served on reference committees, performing outstanding roles. After reviewing some specific results of the meeting, Doctor Hoffman expressed his appreciation and that of Delegation Vice-Chairman Sam Sherman to the entire delegation for untiring efforts and commended the staff for a job well done.

CMA Legal Counsel Howard Hassard outlined the following points to be presented at a hearing before the Senate Subcommittee studying malpractice liability:

(a) The statute of limitations should be tightened to provide a specific commencement point, and to make the period of limitation definite.

(b) The present concepts of privileged communications should be extended to county medical review committees and should include information given in confidence to the State Board of Medical Examiners.

(c) The effect of the doctrine of *res ipsa loquitur* (the thing speaks for itself) should be limited to getting the case before the jury.

(d) A plaintiff should be required to file a nominal bond before filing suit to prevent needless actions.

(e) Set reasonable limits for damages under personal injury awards to insure that premium rates for this type of coverage will not become prohibitive.

(f) Insurance carriers should be permitted to make immediate advance payment to an injured party without admitting liability by so doing.

(g) Some boundaries should be set on the doctrine of "informed consent."

The Council voted to approve these points for inclusion in CMA testimony on malpractice insurance.

Everett Bannister, executive secretary of the Orange County Medical Association, was named to the executive committee of CalPac.

A Committee on Alcoholism Was Created and placed under the Commission on Community Health Service.

The Student Nursing Association of California explained its program for nurse recruitment, which has been awarded a $10,000 grant by the federal government. A CMA representative will serve on the program advisory committee.

In Memoriam

ADLER, ROBERT GEORGE, Auburn. Died 25 November 1967 in Auburn, aged 41. Graduate of Loyola University School of Medicine, Chicago, Illinois, 1950. Licensed in California in 1951. Doctor Adler was a member of the Placer-Nevada County Medical Society.

✣

CRAVIOTTO, JOHN VINCENT, Santa Cruz. Died 24 July 1967, aged 87, of heart disease. Graduate of Cooper Medical College, San Francisco, 1904. Licensed in California in 1904. Doctor Craviotto was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

GREEN, JOHN, Los Angeles. Died 28 December 1967 in Los Angeles of lymphocarcinoma, aged 57. Graduate of University of Toronto Faculty of Medicine, Ontario Canada, 1936. Licensed in California in 1948. Doctor Green was a member of the Los Angeles County Medical Association.

✣

GUYTON, JESSE FRANCIS, North Hollywood. Died 19 December 1967 in North Hollywood of coronary artery occlusion, aged 73. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1917. Licensed in California in 1918. M.D. degree from California College of Medicine, 1962. Doctor Guyton was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

HANLEY, BERNARD JOHN, Los Angeles. Died 27 December 1967 in San Francisco, aged 70. Graduate of the University of Oregon Medical School, Portland, 1925. Licensed in California in 1928. Doctor Hanley was a member of the Los Angeles County Medical Association.

✣

HENNING, BERTHEL HENRY, San Francisco. Died 29 December 1967 in San Francisco of heart disease, aged 69. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1925. Licensed in California in 1925. Doctor Henning was a member of the San Francisco Medical Society.

✣

HEPPNER, GEORGE JOHN, San Francisco. Died 17 December 1967 in San Francisco, aged 63. Graduate of Northwestern University Medical School, Chicago, Illinois, 1930. Licensed in California in 1930. Doctor Heppner was a member of the San Francisco Medical Society.

✣

HIGHTOWER, EMMETT DYSART, Los Angeles. Died 14 December 1967 in San Diego of pneumonia, aged 66. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1927. Licensed in California in 1949. Doctor Hightower was an associate member of the Los Angeles County Medical Association.

✣

KAHN, JACK L., Los Angeles. Died 24 December 1967 in Los Angeles of carcinoma of pancreas, aged 51. Graduate of the University of Chicago, School of Medicine, Illinois, 1940. Licensed in California in 1941. Doctor Kahn was a member of the Los Angeles County Medical Association.

✣

KELSO, GEORGE CAMERON, Pittsburg. Died 23 December 1967 in Saratoga of heart disease, aged 65. Graduate of the University of Minnesota Medical School, Minneapolis, 1931. Licensed in California in 1932. Doctor Kelso was a member of the Alameda-Contra Costa Medical Association.

✣

O'NEILL, JAMES NORMAN, Los Angeles. Died 31 December 1967 in Los Angeles of pulmonary embolism, aged 68. Graduate of Rush Medical College, Chicago, Illinois, 1929. Licensed in California in 1932. Doctor O'Neill was a member of the Los Angeles County Medical Association.

✣

REY, DELBERT F., Palo Alto. Died 15 December 1967 in Palo Alto, aged 59. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1937. Licensed in California in 1938. Doctor Rey was a member of the Santa Clara County Medical Society.

✣

RODDY, JOHN T., Long Beach. Died 27 December 1967 in Long Beach of cardiac standstill due to emphysema, aged 45. Graduate of St. Louis University School of Medicine, Missouri, 1947. Licensed in California in 1947. Doctor Roddy was a member of the Los Angeles County Medical Association.

✣

ROSENTHAL, MILTON, Culver City. Died 11 December 1967 in Los Angeles, aged 50. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1942. Licensed in California in 1946. Doctor Rosenthal was a member of the Los Angeles County Medical Association.

✣

SAWYER, ROY EDWARD, Orange. Died 9 December 1967 in Springhill, Louisiana, aged 37. Graduate of Louisiana State University School of Medicine, New Orleans, 1954. Licensed in California in 1961. Doctor Sawyer was a member of the Orange County Medical Association.

✣

SELESNICK, SHELDON THEODORE, Los Angeles. Died 27 December 1967 in Los Angeles of heart disease, aged 41. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1950. Licensed in California in 1950. Doctor Selesnick was a member of the Los Angeles County Medical Association.

✣

SOBEY, GIFFORD LYNE, Paso Robles. Died 29 November 1967 in Paso Robles, aged 87. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1907. Licensed in California in 1907. Doctor Sobey was a retired member of the San Luis Obispo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

WACHA, VICTOR JAMES, JR., Los Angeles. Died 4 January 1968 of heart disease, aged 42. Graduate of University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1955. Doctor Wacha was a member of the Los Angeles County Medical Association.

✣

WINN, WILLIAM ALMA, Porterville. Died 18 December 1967 in Springville, Tulare County, aged 64. Graduate of Harvard Medical School, Boston, Massachusetts, 1930. Licensed in California in 1934. Doctor Winn was a member of the Tulare County Medical Society.

18th annual regional postgraduate institute

OJAI VALLEY INN
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March 1-2, 1968

WEST COAST COUNTIES

Presented cooperatively by West Coast Counties Medical Societies, University of California at Los Angeles School of Medicine and California Medical Association Committee on Continuing Medical Education. A 12-hour course.

HOST: Santa Barbara County Medical Society
Ventura County Medical Society
Regional Chairman: George J. Wittenstein, M.D.

INSTITUTE FEE: $20.00. For additional information contact Continuing Medical Education office, California Medical Association, 693 Sutter Street, San Francisco 94102. All California Medical Association members and their families are cordially invited to attend.

GUEST SPEAKER: C. Walton Lillehei, M.D., Lewis Atterbury Stimson Professor of Surgery and Chairman, Department of Surgery, New York Hospital—Cornell Medical Center.

PROGRAM THEMES:

BREAST CANCER...MILITARY MEDICINE...CORONARY INSUFFICIENCY...ADOLESCENCE AND THE DRUG PROBLEM...Computer Medicine...Contraception...Management of Rh Sensitized Pregnancies

FRIDAY, MARCH 1

Morning Session

BREAST CANCER

9:00—Introduction—Epidemiology—Lowell E. Irwin, M.D.

9:30—Radiology—Julius H. Grollman, Jr., M.D.

10:15—Surgical Treatment—C. Walton Lillehei, M.D.

10:45—Chemotherapy and Terminal Care—Lowell E. Irwin, M.D.

11:15—Panel Discussion—Question and Answer Session.

Afternoon Session

2:00—Military Medicine—Viet Nam—Brigadier General James A. Wier, MC

3:15—CONCURRENT WORKSHOPS

A 1. Contraception—Richard A. Bashore, M.D.

A 2. Management of Rh Sensitized Pregnancies —Richard A. Bashore, M.D.

B. Neurologic Complications of Cancer—Morton K. Rubinstein, M.D.

C. Computer Medicine—Baldwin G. Lamson, M.D.

SATURDAY, MARCH 2

Morning Session

EVALUATION AND TREATMENT OF PATIENTS WITH CORONARY INSUFFICIENCY

9:00—Introduction—Mark E. Winfield, M.D.

9:30—Radiology—Julius H. Grollman, Jr., M.D.

10:00—Medical Aspects—Mark E. Winfield, M.D.

10:45—Surgical Aspects—C. Walton Lillehei, M.D.

11:15—Panel Discussion—Question and Answer Session.

Afternoon Session

2:00—Adolescence and The Drug Problem—J. Thomas Ungerleider, M.D.

3:15—L.S.D.—Problems and Prospects
Video Tape—Contrasting views of the current uses and abuses of this fantastic chemical.

Expense and Physician Motivation

SAUL J. ROBINSON, M.D.

Member of the Scientific Board and the Committee on Continuing Medical Education, California Medical Association

No one subject has received more recent attention than the motivation of the practicing physician to continue his medical education after his formal training has been concluded.

It is generally agreed that in order to keep up with advances in medicine, a physician must in some way remain exposed to current medical events. Many suggestions have been made and are being utilized to obtain this goal; among them can be included the reading of medical journals, attendance at meetings, including local hospital rounds, monthly, semi-annual and annual meetings in the community, or national meetings and, finally, one day, two day, weekly, or even longer courses or lectures and conferences sponsored by medical centers or national organizations.

In order to attend the conferences away from home, the physician must first initiate a program to see that his patients receive adequate care while he is gone. This is simpler in a group practice, but can also be attained by agreement among physicians to cover each other while attending meetings or conferences.

Another one of the reasons for non-attendance aside from lack of time may be the expense involved. Not only must the physician obtain supervision of his practice while away, but the necessary expenses of maintaining an office must be continued over and above the expense of attending a meeting. In themselves, travel expenses, hotel expenses, continually increasing registration fees may come to a considerable amount and deter the less motivated from becoming a participant in what is now a voluntary gesture to maintain his competence. Does the financial burden (added to inconvenience) act as a deterrent to such attendance at a continuing medical education conference, even though it is a deductible expense and frequently combined with a vacation? To the strongly motivated physician the rewards outweigh the expense. To the physician, however, who needs a greater stimulus, the increasing cost of such medical adventures may be the reason for non-attendance, thereby penalizing, even though unfortunately, his patients.

It is the patient who benefits from such self-imposed study by the physician. There are no criteria by which patients or fellow physicians may judge the relative ability of the physician who does not attend such meetings or conferences. Should then the physician be required to pay all of the costs of attending such conferences? While most of these fees are reasonable, there seems a tendency to charge higher and higher registration fees for such courses without necessarily better facilities, better organization, or better courses. There has also been a tendency to have these courses at the most expensive hotels with not only higher registration fees, but rather extreme charges for "luncheons," etc. over and above the initial fee.

If answers to a questionnaire recently sent to physicians by the California Medical Association should reveal that the cost of continuing education is a factor in deterring physicians from attending, then it behooves those concerned with physician education to see that some form of financial aid is developed, that the necessity for high costs be carefully documented, and that the recipient of such education might well merit some financial incentive to tempt him to continue his medical education.

The medical student is becoming more and more subsidized in his education as everyone realizes the importance of maintaining an adequate number of physicians to care for the health needs of the country's population. It is no less important that some source of funds be utilized to help practicing physicians receive their continuing education. It is not too much to suggest that physicians might even receive a bonus for devoting the time and effort to such studies so that their patients may receive the benefits of such educational efforts now received only by personal and financial sacrifice on the part of the physician.

A grant for continuing medical education should be easily available to the physician, as are grants for other fields of endeavor in medicine. The very least of the rewards for such inducement would be good patient care.

Reprint requests to: 2300 California Street, San Francisco 94115.

application for HOTEL ACCOMMODATIONS

NINETY-SEVENTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 23-27, 1968

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House of Delegates Opening Session, Mark Hopkins, Saturday evening, March 23; Scientific Sessions, Fairmont Hotel, begin Sunday morning, March 24.

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Mining Camp Medicine

Physician-Adventurers of Early California

HOWARD K. LINDER, M.D., *Sacramento*

IN THE EIGHTEEN-FIFTIES, in the wake of the great California Gold Rush, an eastern writer traveled the length of the famous Mother Lode. He reported to his readers: "The entire countryside resembles a battlefield. The earth has been torn up for hundreds of miles along the banks of rivers and streams. Heaps of sand and gravel dot the landscape presenting a remarkably dry and sterile appearance. Sagging shafts perforate the hillsides. The great placer mines of California are practically worked out."[10]

This eye-witness account may well have surprised easterners, but it was hardly news to thousands of frustrated Forty-niners. Stranded amid the exhausted placers, they wandered aimlessly through the Sierra foothills searching for new diggings. Many had become discouraged and returned to their homes in the East with pockets empty. Some had settled down as merchants in the cities and as ranchers in the valleys of California. A few, and they were indeed few, had made their strikes and retired as wealthy men. There remained a nucleus of hard-nosed Argonauts who refused to give up the great adventure—the chase for the pot of gold at the end of the rainbow. Among them was a liberal sprinkling of physicians who would spend the next twenty-odd years following the great cycle of boomtowns extending from California to western Nevada and back to California again.

It has been estimated that upwards of fifteen hundred physicians joined the Gold Rush. The title "Doctor" was often used loosely on the American frontier, and in the California mining camps every conceivable type of "healer" appeared. Among the qualified graduates of eastern medical schools and European centers marched an army of eclectics, hydropaths, phrenologists, botanics and some who swore allegiance to no particular school of thought but merely issued themselves a diploma and hung out a shingle. Of this array of talent and fraud, many returned to the civilized east after "seeing the elephant." There they resumed their practices and there they could in later years, reminisce, as did one Doctor M'Collom, over the greatest adventure of their lives. He wrote: "I went to see . . . it was wild . . . a hare-brained adventure . . . in looking back there are no regrets. . . . With California, and all that is in it . . . I quit even."[7]

But many gold rush physicians remained in California. Some settled in the booming cities of San Francisco and Sacramento. Others established practices in the smaller towns springing up throughout the state. From their numbers would come the leaders of medicine on the Pacific Coast who would organize professional societies, establish schools of medicine, and constitute the medical backbone of the new state.

But also among these pioneer men of medicine was a small army of physician-adventurers, both regular and irregular, who chose to remain in the gold fields and to adopt the mining camp as a way of life. They were a colorful lot. They left no monuments bearing their names nor do they appear as the founding fathers of the various medical soci-

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eties. They remain buried as mere footnotes in rare historical accounts, but they were, nevertheless, an integral part of the medical history of California.

If conditions on the Mother Lode were primitive, the medical atmosphere was chaotic. A certain degree of courage was necessary to hang out a shingle in a mining camp, and considerable stamina was required to persist. The faint-hearted soon departed. A young British surgeon arrived early on the scene in Placerville (it was called Hangtown at the time). Purchasing a second-hand canvas tent, he partitioned it into two rooms, one for living quarters, the other for his "surgery." He then hung out a new sign:

> "Dr. Edward Willis. M.R.C.S. Surgery and Physic in all branches. Draws teeth painlessly. Bleeds. Advice gratis."

Doctor Willis drew more than teeth. Into his new office stormed the only member of the Hangtown Medical Society, a Doctor Hullings, who enjoyed a medical monopoly in the mining camp and meant to keep it that way. A brawler and a bully, Hullings frequented the numerous saloons and was known as an accomplished artist with the knife and the pistol. He was often too drunk to detect a pulse. Nature had endowed him with an incredible constitution, which enabled him to shake off the effects of a debauch and to labor like a madman, purging, bleeding and bandaging until sufficient reserves were accumulated to permit another prolonged spree. Doctor Hullings' approach was direct. The young Englishman was informed that he was an intruder—worse, a claim jumper. Swaying slightly, and smelling of strong spirits, the irate physician demanded credentials. Diplomas from the Universities of London and Edinburgh were produced. The Englishman was astounded when Hullings tore the documents to shreds and compounded the outrage by lofting a mouthful of tobacco the length of the room to splatter on a batch of pills.

In the absence of machinery for law and order, disputes in the early gold camps were often settled by unique and sometimes spectacular methods. Dueling was fashionable, and Hangtown boasted its own refinement. When Doctor Willis issued the challenge, both physicians were led to an abandoned diggings, where they were lowered into opposite ends of a deep trench. The referee clapped his hands, and the combatants blazed away. The system was foolproof—discouraging a last-minute bolt by the chicken-hearted, offering a degree of protection to witnesses from stray bullets, and affording an element of suspense while waiting for the survivor to appear. In addition, this modification assured a ready-made grave. When the smoke cleared, a grim-faced Doctor Willis emerged amid cheers and immediately took over the operation of the Hangtown Medical Society.

Courage of another type was required of Dr. C. P. Aiken of Downieville. In 1851 he found himself in the unfortunate role of attending physician for the famous "Juanita," a youthful belle of Spanish descent who was to become the only woman to be hanged in the history of the Gold Rush. The facts in this celebrated case have been the subject of considerable debate. That Juanita was Mexican, Peruvian, or Chilean has never been proven. Accounts vary, describing her as a dance-hall girl, a frail beauty, a vicious prostitute. One fact is clear: By her own admission, she had deftly inserted a knife between the ribs of one Jack Cannon, bringing to an end the popular Australian's career. Downieville was outraged. An open-air trial was immediately held in the town plaza. It was a popular court, a device common in the early mining camps which often bordered on mob action. The atmosphere was not improved when Jack Cannon's body was placed nearby in a tent where the excited populace could view the gaping wound. What began as a trial soon erupted into a brawl. A young lawyer with considerable fortitude mounted an empty whiskey barrel and pleaded the young woman's case. The crowd would have no part of his argument. A red-shirted miner kicked the barrel from under him, eager hands lifted the defense counsel from the ground and dragged him to the edge of town. There was another witness for the defense. Panic-stricken, Doctor Aiken faced the crowd. He was, he blurted out, Juanita's physician. The announcement was received with a thunderous silence. Then he dropped a bombshell. The accused was, he stated, "enciente," or, in the words of the Yankee, "with child."

Pandemonium erupted. Doctor Aiken instinctively felt of his neck as the mob roared for the same. In the frustration over this turn of events, cooler heads prevailed and it was decided to obtain consultation. A specialist was summoned. The examination took place in a small frame house nearby. As the two physicians reevaluated the case, the mob grew restless, and shouts of "hang

'em all" penetrated the flimsy walls. No neatly-typed transcript remains of that consultation. Left to the imagination is the effect of the tension and terror on examining fingers. One fact is history: When they emerged from the cabin, the specialist announced amid cheers that, in his opinion, Juanita was not pregnant. Doctor Aiken stuck to his diagnosis. But Juanita was hanged from a bridge over the Yuba River, and her attending physician was escorted to the edge of town by a grim-faced crowd, ending his career in Downieville.

Medical scoundrels infested the gold fields. Dr. Thomas J. Hodges found his way to California by way of the war with Mexico. Born in Rome, Tennessee, he joined the army as either a contract surgeon or simply a hospital orderly. Certainly he enjoyed a medical exposure of sorts, for he appeared in the various camps on the Mother Lode as a physician. He also tried his hand at gold mining. He found neither pursuit rewarding and took to the saloons, where he developed a fondness for raw frontier whiskey and revealed a certain deftness with cards. Low on funds, he wandered down to Mariposa, where he came upon a herd of mules, separated them from their Mexican owner, and was back in business. This act launched him on a new career which, although more promising, soon landed him in the state prison. Thomas Hodges was not discouraged. He took advantage of the confinement to complete a graduate course under the direction of one Bill Gristy, an accomplished bandit and badman. Feigning illness, he escaped from the prison hospital, changed his name to Tom Bell, and entered into his new profession with enthusiasm and skill.

Tom Bell and his newly organized gang specialized in stage holdups. Operating out of the foothills north of Auburn, they also ran off cattle, waylaid lonely travelers, and blew safes. As the depredations continued, the gang became notorious, and authorities were under considerable pressure to bring them to justice. Lawmen enjoyed one advantage. Bell was a striking figure. He was tall, had flowing sandy hair, and a long-past saloon brawl had left him with a badly smashed nose, a combination making for easy identification. The problem was catching up with Tom Bell.

The gang was highly organized, with hideouts and secret passwords. Often its members committed robberies simultaneously miles apart. Reportedly, on one occasion at least, the bandit leader remembered he was a physician. During a holdup, one of the gang shot a traveler. Tom Bell dismounted from his horse, removed the bullet from the victim and dressed the wound. He then galloped off to new adventures. The end finally came with the attempted holdup of the Camptonville stage near Marysville. On this occasion, the passengers fought back, and a running gun battle ensued in which the driver was wounded and a passenger killed. But the stage got through and the outlaws were foiled. Posses chased Bell down into Tulare county, where he was captured and hanged. He became a legend on the Mother Lode. One old-timer recalled, "As a doctor he was as gentle as a kitten, but as a bandit he was a bragging, swaggering bully."

One medical imposter gave up a flourishing career in crime to settle down in early-day Stockton to practice medicine. Captain Yoemans (his true name remains a mystery) was a noted leader of a band of Mexican outlaws operating throughout Southern California. Exuding charm and fluent of speech, he hung out his shingle as "Doctor Roberts." He was, he announced, an Englishman by birth and had come to California by way of Mexico. Obviously a gentleman, he became popular in the small social circle, and as his practice flourished, he happily invented another degree. Doctor Roberts claimed he was also a lawyer, thus offering the community a wider spectrum of professional coverage. He proceeded to impress the legal fraternity. Displaying an unusual knowledge of Spanish estate law, he eloquently argued a case over a disputed land title and won a favorable verdict for his client. He was rewarded with a fat fee. He became a close friend of David S. Terry, the young Southern lawyer who was to become a Supreme Court judge and the survivor of the famous Terry-Broderick duel.

As one triumph followed another, Doctor Roberts was well on his way to a successful dual career, when disaster struck. Called into consultation on a member of one of the more important local families, he displayed an appalling ignorance of basic medical concepts. Eyebrows were lifted. Whispered rumors spread around the town. His patients began to dwindle away. One local merchant, his memory prodded by the recent turn of events, suddenly recalled a stagecoach holdup of the past. The gunman, he remembered, bore a remarkable resemblance to Doctor Roberts. After a quick investigation, the physician was exposed as an im-

poster and a former highwayman who had terrorized stage lines from Panama to San Francisco.

No one was more surprised than David Terry. Defending his friend's reputation, he challenged the merchant to a duel. While seconds were being named and weapons were selected (Terry chose pistols at ten paces), Doctor Roberts quietly decamped. The duel was cancelled. The entire mystery was solved later when a Wells Fargo stage was held up in the south. One of the bandits was captured and confessed that their leader was the notorious Captain Yoemans, recently returned to banditry after a tour of respectability in Stockton.

With the exhaustion of placer mining on the Mother Lode, the gold rush period came to an end. To the stranded Argonauts, mining in the Far West appeared to be dead. Two Irishmen changed that. In 1859, beyond the Sierra over in Utah Territory, soon to become Nevada, Peter O'Riley and Pat McLaughlin struck it rich on the sterile slopes of Sun Mountain. Thousands of fortune-seekers poured over the Sierra to Virginia City. In the front ranks of this stampede marched a number of physicians who, having settled for a life in the mining camps, were prepared at a moment's notice to haul down their shingles, pack their few belongings and tramp off to a new discovery. They spent most of their careers in the boomtowns of the Far West, where, in effect, they practiced a profession within a profession. After Virginia City, a cycle of "strikes" would carry them to Aurora, Austin and Treasure Hill in Nevada, with a dozen lesser stops in between. The trail would lead back to California again, to Panamint, Darwin and Bodie.

Dr. Simeon Bishop was one of these professionals. He spent his entire life in the mining regions of California and Nevada. He practiced medicine in Columbia, Sutter Creek, Angels Camp and Iowa Hill. He joined the "rush to Washoe," opening an office in Virginia City, where he became quite prominent. He met and married the daughter of Wells Drury, a famous Nevada journalist. Bishop had an unerring eye for mineral. In 1876, while visiting a patient near Pyramid Lake, he spotted a specimen of ore on a table. Unable to conceal his excitement, he examined the rock and plagued the household until he learned where it had been found. His practice forgotten, he led a small army of miners off to the new mineral field, where they established a boomtown. But the ore petered out, the excitement died down and he returned to his medical duties.

Doctor Bishop hated cities. He tried it once. He moved to San Francisco, where he attempted to practice in a more civilized atmosphere. But he couldn't stand it. "A home in the city," he reported, "is made up of a man, somebody else's wife, and a dog—all in one apartment." He returned to the mining camps. There he never bothered to keep books. He rarely sent bills. But he always claimed that his reward came later in life when, as superintendent of an asylum for the insane in Reno, he received a monthly check in five figures from a grateful inmate.

Dr. George Hoyt was nearly seventy years old when he appeared in Virginia City. He was a printer by trade, a physician by profession. As experience had taught him that mining camps were often flooded with doctors, he went to work for the *Territorial Enterprise,* Nevada's pioneer newspaper. There were certain advantages to life as a tramp printer. One of them was that immediate employment was almost always assured. In addition, as today, physicians were expected to maintain a degree of temperance, whereas members of the newspaper fraternity, notoriously a hard-drinking lot, were cheered for their exploits with the bottle. Hoyt became an associate of Mark Twain and Bill Gillis and spent many an evening with them at wine in the local pothouses. On one occasion, printer Hoyt was reminded that he was a physician. A smallpox epidemic swept the Comstock. Doctors were swamped. Doctor Hoyt hung up his printer's apron, dusted off his black bag and joined in the medical rounds. Working furiously day and night, he himself contracted the disease. Mark Twain and Sam Gillis were lounging on C Street one day when they spotted the weary doctor. They greeted him.

"Go back, you fools," Doctor Hoyt called. "I've got the pox. Don't come near me."

He took a watch and chain from his pocket and placed them on the ground.

"I'm going to the pest house. If I die, I want one of you to have these. You can draw straws or pitch a coin for them. Goodbye, boys."[6]

But Doctor Hoyt recovered, and when the epidemic subsided he returned to his job as a printer.

Before the California legislature passed an anti-quackery law in 1876, mining camps were a bonanza for medical irregulars. One bogus doctor, whose name has been lost to history, arrived in

Bodie by a devious route. He had been the proprietor of a stage station in the Pahranagat Valley of Nevada when, in 1866, Governor H. G. Blasdel stopped over for the night. After dinner, the honored guest became quite ill. As there were no doctors within a hundred miles, the station manager did what he could to help. He noted that the symptoms torturing the governor resembled a condition common to horses, one that he was often called upon to treat. Repairing to the stable, he fetched a bottle of his "Equine Elixir" and with a good deal of prodding and prying administered a stiff jolt to the patient. Somewhat to his surprise, the governor arose the next morning in the best of health and, praising the talents of the station keeper, continued his journey.

But fate proved cruel to the one-time hero. By 1876, he had lost his stage business and had appeared in Bodie, broken in spirit as well as in purse. Recalling his flair for therapeutics, he hung out a shingle and, adding the letters M.D., he was in business again. As his practice flourished, he was soon treating aches and pains with results as gratifying as when he had nursed his horses afflicted with the epizootic. But again misfortune struck. He was hauled into court and charged with violating the new anti-quackery law. He proved to be a man of many talents, for with the eye of a barrister he spotted a grandfather clause in the act which specifically exempted anyone who had engaged in the profession, by prescribing or treating, for more than ten years before enactment of the statute. He testified that he had prescribed and treated and had, indeed, effected a cure of the Governor of Nevada eleven years earlier. He was acquitted when he triumphantly produced, as evidence, a crumpled newspaper account of the incident.

Mining camp physicians sometimes faced situations that would have curled Wyatt Earp's moustache. Dr. J. W. Gally settled down in the mining camp of Tybo, Nevada, in 1866. He was the town's only physician, and as he prospered he became part owner of the Two Gee mine and acquired a cattle ranch. Popular and respected, he was nominated for the office of justice of the peace. Tybo was booming and law enforcement was weak, a combination that created an agreeable atmosphere for some of the worst scoundrels on the Pacific Coast. This tough element was pleased with the prospect of a harmless physician occupying the bench. They trooped out to vote for him, and the doctor was elected in a landslide.

But Doctor Gally dispensed justice as objectively as he had prescribed potions and powders. He proved immune to politics and bribery, and even threats failed to influence his verdicts. A new era had arrived in Tybo. In some quarters it caused near panic. On one occasion, chaos broke out in the courtroom when opposing parties drew pistols and threatened to settle the argument in a gun battle. In the uproar, the gavel pounded loudly. All parties turned to view the judge holding a shotgun, hammers cocked, and the muzzle trained on the courtroom. Somewhat shaken, all returned meekly to their seats. At this turn of events, the local toughs gradually departed town in search of greener pastures. Soon, Tybo's gold disappeared from her ore and the population drifted away. Doctor Gally sold out his interests, packed his family and belongings in a wagon, and headed for Watsonville, California, where he hung his shotgun over the fireplace and returned to the practice of medicine.

Bodie was probably the wildest mining camp in the history of California. The discovery of rich gold deposits there in 1877 sent thousands of eager boomtowners into the sagebrush hills of Mono County, where affairs of the knife and the pistol were of almost daily occurrence and led to the claim that Bodie could boast a "man for breakfast" every morning. Her medical men proved equal to the challenge. Arriving early upon the scene, Doctor T. S. Blackwood was sent into action immediately. He presided over the demise of "U. P." Jack Breslin, who had failed to survive a gun battle. U. P. Jack (the initials were derived from the Union Pacific Railroad, whose construction camps he had terrorized before drifting west) had staked out a claim as the camp's chief thug. In a battle with one James Blair over the coveted title, the two toughs held onto each other while blazing away with their pistols. Blair won the war but was hauled off to Doctor Blackwood's office, where the frontier physician boldly amputated a shattered arm. The local press reported, "Doctor Blackwood has as adornments in his office pieces of bone extracted from Blair's arm. He fondles them with the greatest delight. The operation was a success."[2]

The flamboyant Blackwood was constantly appearing in the news. One day he kicked up a nugget at the end of Main Street. Investigation re-

vealed more evidence of gold. During the night, he constructed a shanty in the street and surrounded it with a wire fence. Dawn brought considerable excitement. Jumping claims was common, but street-jumping was a new twist. All Bodie was furious. The fire bell clanged and irate citizens gathered. A demand for the withdrawal of the obstruction was issued in colorful frontier language. From his shanty fort came the doctor's reply, "Go slide on your ears."[1] Thereupon the citizens attacked, and within minutes the physician's castle was a wreck. He was fortunate to escape with his life.

Doctor Blackwood's final escapade in Bodie resulted from his scientific turn of mind. It proved his undoing. In the pursuit of knowledge, he presided over a refresher course in anatomy. Sessions were held in an old cabin at the edge of town and always at night. Secrecy was essential, for cadavers were obtained from the graveyard. When the courses ended, the remains were disposed of in abandoned shafts that dotted the hillside. Unfortunately, a miner stumbled into one of the old shafts. Panic ensued. The newspapers reported the grisly murder of a young woman, and while mothers whisked their young from the streets the local legal machinery ground into action. The mystery was solved in a most unexpected manner. During the excitement, a patient had called on Doctor Blackwood. While reciting her symptoms, she had glanced at a skull adorning his desk. Suddenly she shrieked, bolted from the office, and dashed down Main Street crying, "My god, it's Millie. I'd know her teeth anywhere."[2]

Gunplay and knifings Bodie knew and tolerated, but grave-robbing was a horror new to the community. Several doctors suddenly left town on extended vacations, not to return until the atmosphere cleared. But Doctor Blackwood's flight was permanent, for he never again set foot in Mono County.

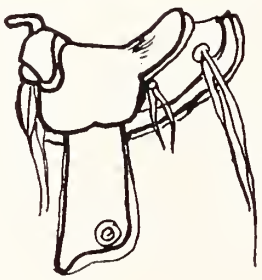
With the decline of Bodie in the early eighteen-eighties, mining excitements, for the most part, came to an end in California and the Great Basin, not to be revived again until Jim Butler and his burro discovered Tonopah after the turn of the century. Many mining camp physicians drifted away to Tombstone, Deadwood and Butte. Some retired to the lush coastal valleys of California. Few had found the pot of gold at the end of the rainbow. The majority ended their careers with little in the way of material gains. There is no evidence of regret. It is difficult to equate this strange affliction with present-day standards. Perhaps the phenomenon was best defined by Shorty Harris, a celebrated prospector of a later era. Shorty had "struck it rich" several times, only disdainfully to throw away his fortunes. In his twilight years, a reporter found him living alone in the abandoned camp of Ballarat, penniless, but preparing a trip into the Panamints, where he knew of a promising ledge. The writer suggested that the old prospector might well be a millionaire—perhaps worth $10,000,000—had he lived his life differently. Shorty looked with disgust at the man from the city.

"Who in hell wants $10,000,000," he growled, "It's the game, man—the game."[3]

The old mining camp doctors would have agreed.

REFERENCES

1. Bodie Free Press, Bodie, California, Jan. 1880 to June 1882.
2. Bodie Standard, Bodie, California, 6 Feb. 1878, to 30 June 1881.
3. Caruthers, W.: Loafing Along Death Valley Trails, Death Valley Publishing Co., Shoshone, California, 1951.
4. Drury, Wells: An Editor of the Comstock Lode, Pacific Books, Palo Alto, 1936, p. 31.
5. Dunlop, Richard: Doctors of the American Frontier, Doubleday and Co., New York.
6. Gillis, W. R.: Memories of Mark Twain and Steve Gillis, The Banner, Sonora, California, 1924, pp. 82-83.
7. Groh, George W.: Gold Fever, William Morrow and Co., New York, 1966, pp. 289-290.
8. Inyo Register, Bishop, California, 20 July 1916.
9. Jackson, Joseph Henry: Anybody's Gold, D. Appleton-Century Co., New York, 1941.
10. Langworthy, F.: Scenery of Plains, Mountains and Mines, Argonaut I:22, Mar. 1877.



Evaluation of 100 Esophageal Motility Studies at a University Medical Center

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■ *100 esophageal motility studies on 88 consecutive patients referred to the University of California Medical Center were analyzed. Diagnoses of achalasia, diffuse spasm of the esophagus, scleroderma, hiatal hernia and other conditions were made from the motility tracings. The motility tests have been found to be most helpful in differentiating various disorders of swallowing and thoracic pain of unknown cause.*

FOR THE PAST DECADE, esophageal motility studies have become an increasingly popular and useful source of information for physicians in evaluation of patients with motor disorders of the esophagus and thoracic pain of uncertain cause. In conjunction with barium swallow studies of the esophagus, esophagoscopy, acid perfusion tests and cytologic examination of esophageal washings, esophageal motility tests have assumed great importance in pinpointing the nature of the swallowing disorder. Motility studies have also been used with increasing frequency in preoperative evaluation of esophageal motor diseases and postoperative follow-up studies.

Since 1964, when the esophageal motility laboratory was first opened at the University of California Medical Center, more than 300 esophageal motility tests on patients referred to the medical center have been performed. This report includes an analysis of 100 studies done on 88 consecutive patients referred during the years 1964-1965 because of swallowing difficulties or pain in the chest of unknown origin.

From the Department of Medicine, Gastroenterology Unit, University of California School of Medicine, San Francisco.

Reprint requests to: Sacramento Medical Clinic, 2615 Eye Street, Sacramento 95816 (Dr. Wilbur III).

Methods

A four channel Model 150 Sanborn recorder with amplifiers and Sanborn Model 268A transducers located outside of the body was used in this study. Amplifiers and transducers are needed to transmit the extremely low pressures obtained within the esophageal lumen to the heat stylus of the recorder so that the tracing is large enough for accurate interpretation. Simultaneous pressures are detected at three areas within the esophagus 5 cm apart.

A tiny, water-filled latex balloon on the end of a polyethylene catheter and two open-tipped polyethylene catheters with holes cut in their sides are tied together by a thread. This pressure-sensitive unit is easily swallowed by the patient. There have been no complications of the procedure in over 300 tests. The method is similar to that originated by Code.[1]

The balloon, 0.5 cm in diameter and 1 cm long, is used because it helps to bring out and record extremely small changes of pressure within the gastroesophageal and pharyngoesophageal sphincters. The balloon is made in the laboratory by dipping an aluminum mold of proper dimensions, two or three times, into liquid latex at room tempera-

ture. Each coat of latex is allowed to dry as evenly as possible so that the balloon's wall thickness will be uniform.

A size PE 190 polyethylene catheter is first completely filled with water. A latex balloon is then tied to the catheter by thread under water so that no air bubbles, which might dampen the low pressure system, are present. If the neck of the balloon is too wide for a snug fit on the size PE 190 catheter, then a short adapter, such as size PE 200 tubing, may be used.

Two other PE 190 tubes, with tiny holes cut in their sides at 5 and 10 cm from the center of the balloon, are then tied together with the balloon tipped catheter to form a single unit. Next, the three recording tips are standardized so that 0.5 cm vertical deflection of the heat stylus is equivalent to 10 cm of water pressure.

After fasting so that food will not clog the open-tipped tubes, the patient swallows the tied together catheters while in the sitting position. After the balloon has passed through the upper sphincter of esophagus, the unit is placed to the side of the mouth between the teeth and the cheek to lessen the patient's tendency to gag and possibly to bite the soft, water filled polyethylene catheters. As the unit is small, no local anesthetic or pre-medication is needed.

After the unit is swallowed, the patient is asked to lie supine on a heavy, steady table which may be raised so that the level of the patient's esophagus is equal to that of the transducers. Next, all of the air bubbles and occasionally mucus plugs are flushed out of the two open tipped catheters by filling them slowly with water. A pneumograph, to record respiration, is then attached around the lower part of the patient's thorax. The motility study starts with the unit in the fundus of the stomach.

Fluoroscopy is not required since a positive deflection of the heat stylus on inspiration shows that the recording tips are in the stomach. A negative deflection on inspiration indicates that the catheter tips are within the esophagus. As the unit is slowly pulled out of the patient's mouth, distances from the incisor teeth are accurately measured from a tape that has previously been placed at 60 cm from the center of the balloon.

The resting study is the first portion of the test. The catheter unit is slowly pulled from the stomach, through the gastroesophageal sphincter, and into the lower esophagus at 0.5 cm intervals. The paper speed in the resting study is 1 mm per second. The patient is asked not to swallow, if possible, during the resting study, since a swallow may interfere with the accurate measurement of resting pressure in the gastroesophageal sphincter. An occasional swallow in the resting study is often unavoidable.

The gastroesophageal sphincter[6] is seen as a zone of increased pressure located 35 to 45 cm from the incisor teeth. As soon as all three recording units have passed entirely through the gastroesophageal sphincter, the resting study is completed. A single dry swallow is then recorded to prove that all three pressure-sensitive tips have indeed entered the lower esophagus.

The recording unit is then pushed back into the stomach for the second portion of the test, the swallowing study. The paper speed of the recorder is increased to 2.5 mm per second for this portion of the test. Once again, the unit is slowly pulled orad at 0.5 cm to 1 cm stations in the lower sphincter area, with dry or wet swallows taken at each station. Wet swallows are performed by giving the patient approximately 5 ml of water before asking him to swallow once. One purpose of the wet swallow is to record maximal relaxation of both sphincters in response to swallowing.

The gastroesophageal sphincter is characterized chiefly by relaxation in its lower or subhiatal portion and by contraction in its upper or suprahiatal portion.[7] Relaxation of the gastroesophageal sphincter is absent in achalasia. At least one good swallow should be performed with the balloon

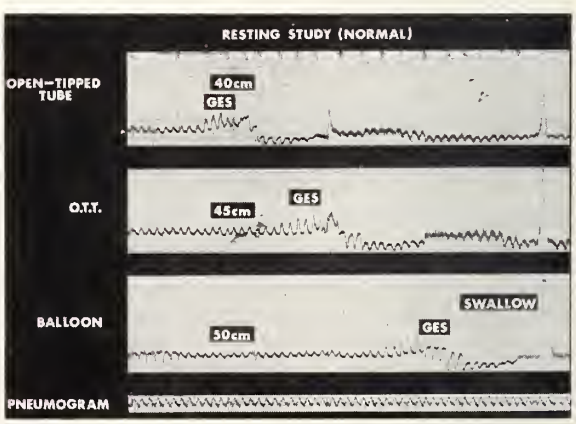


Figure 1.—Esophageal motility study reveals the resting pressure and length of the gastroesophageal sphincter (G. E. S.) in a normal subject. The distance is measured in centimeters from the incisor teeth. Mean fundic pressures shown on the left side of the record are greater than negative esophageal pressures on the right.

tipped catheter precisely in the gastroesophageal sphincter.

Another purpose of the wet swallow is to see the maximal amplitude of the deglutition wave at any point within the body of the esophagus. In addition to swallowing waves and normal respiratory excursions, cardiac pulsations are often recorded when the balloon lies in that portion of the esophagus next to the heart.

The swallowing study continues upward through the entire body of the esophagus with swallows taken at each 1 or 2 cm station. The pharyngoesophageal sphincter is easily seen as a high pressure zone 12 to 20 cm from the incisor teeth characterized by relaxation preceding a rapid contraction. The swallowing study is completed by a swallow when at least one recording tip of the unit is in the pharynx. The rapid contraction of the striated muscle in the pharynx, upper sphincter and upper portion of the esophagus is contrasted greatly with the slower swallowing contractions of the smooth muscle in the remainder of the esophagus.

Results

Normal Subjects

In this study of 100 consecutive motility records in 88 patients, 28 showed no esophageal motor abnormalities. An example of a normal resting pull-through study of the gastroesophageal sphincter is shown in Figure 1.

The length of the gastroesophageal sphincter averaged 3.8 cm as measured by the open-tipped catheters in normal persons. The mean length of

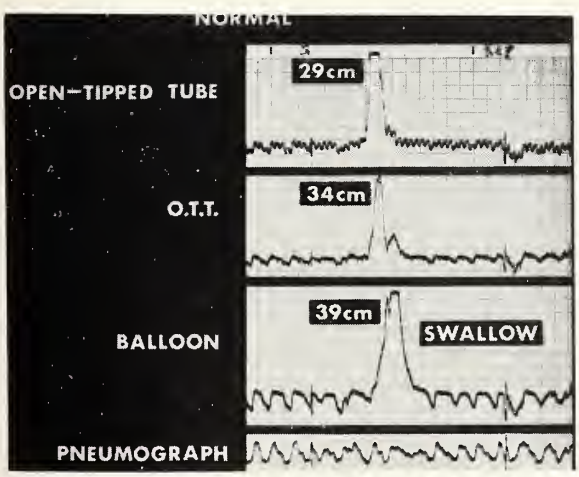


Figure 2.—Swallow in a normal subject shows good peristaltic progression of swallowing wave as recorded in the lower esophagus.

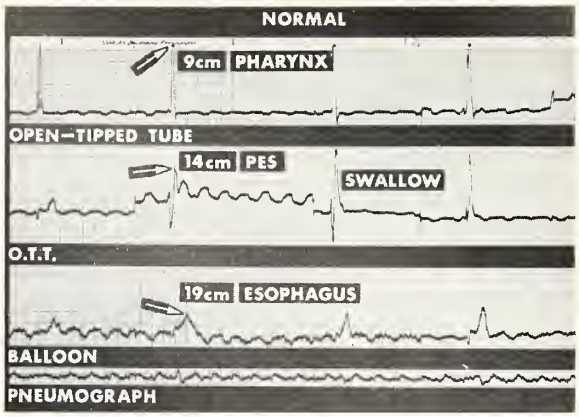


Figure 3.—Pharyngoesophageal sphincter (P. E. S.) of a normal subject shows relaxation followed by contraction. The striated muscle of the pharynx reveals a shorter duration of contraction than that of the esophagus.

this sphincter in normal subjects as recorded by the balloon was 4.8 cm, the additional centimeter being accounted for by the 1 cm length of the balloon itself. The mean pressure of the gastroesophageal sphincter above mean fundic pressure of the stomach was 12.2 cm of water in normal subjects as measured by the open-tipped catheters. The mean pressure of the gastroesophageal sphincter as recorded by the balloon was not as consistent as those pressures recorded by the open-tipped tubes.

Slight differences in the thickness of balloon walls probably accounted for more variation in pressure readings. However, pressures recorded by the balloon in the gastroesophageal sphincter were always higher than that measured by open tipped tubes in the same patient. The mean pressure as recorded by the balloon in normal subjects was 20 cm of water above mean fundic pressure.

The swallowing response of a normal subject in the body of the esophagus is shown in Figure 2. The swallowing wave reaches the proximal open-tipped catheter first, the distal open-tipped tube second, and the balloon-tipped catheter third in normal peristaltic progression. The deglutition sequence in a normal subject in the pharyngoesophageal sphincter (Figure 3) shows relaxation followed by contraction that is much more rapid than that found in the lower esophageal sphincter.

Achalasia

Seventeen patients in this study had achalasia or cardiospasm (Figure 4). This motor disorder

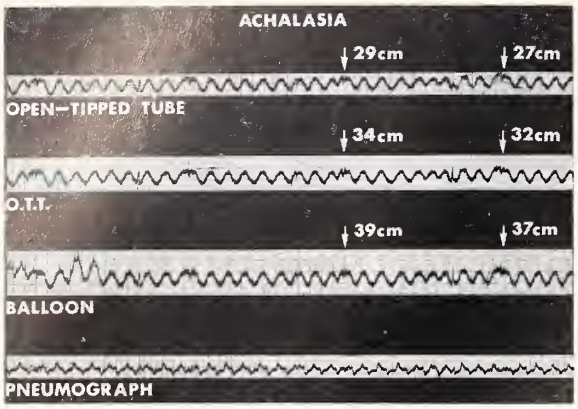


Figure 4.—Tracing of patient with achalasia shows very weak and simultaneous (aperistaltic) swallowing waves. Swallows are identified by arrows.

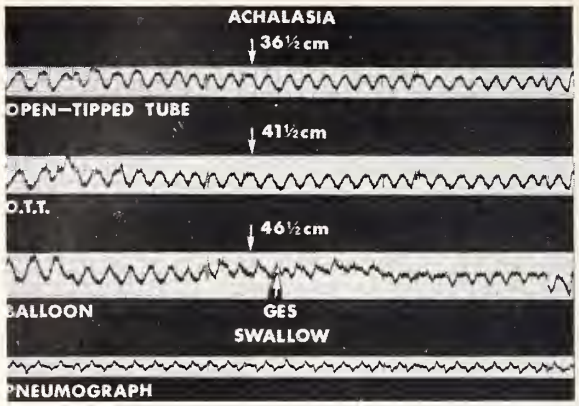


Figure 5.—Tracing of patient with achalasia with the balloon at the gastroesophageal sphincter. The sphincter shows no relaxation with swallowing in this disease.

of unknown cause is characterized by degeneration or absence of Auerbach's myenteric plexus within the esophagus. The classic greatly dilated esophagus of advanced achalasia as seen on a barium swallow is easy to identify. However, esophageal motility studies give physicians an opportunity to diagnose achalasia early, before this dilatation occurs, during the period when results of treatment are much more satisfactory.

The length of the gastroesophageal sphincter in this study averaged 3.1 cm in achalasia, as measured by the open tipped catheters. The mean pressure of the gastroesophageal sphincter was 13.6 cm of water in achalasia, compared with the normal subject's 12.2 cm of water as recorded by the open tipped tubes. This finding confirms that there is not an excessively high pressure or "spasm at the cardia" in all but extremely rare cases of achalasia. Therefore the old term *cardiospasm* should not be used in this disease.

There is no peristalsis found in achalasia (Figure 4). Weak, simultaneous and occasionally repetitive waves are seen throughout the body of the esophagus. Early in the disease, these simultaneous swallowing responses are vigorous and of normal amplitude. If possible, it is best to begin treatment during this early phase. Later in the disease, the simultaneous swallowing responses become weaker and eventually almost complete motor failure may take place.

In achalasia the gastroesophageal sphincter does not relax following a swallow (Figure 5). In this disorder, the exaggerated response of the esophageal musculature to the drug metacholine chloride (Mecholyl®) is characteristic (Figure 6). After 5 to 7.5 mg of the cholinergic drug Mecholyl is given subcutaneously, the intraesophageal pressure rises greatly in achalasia and is recorded in centimeters of water above the baseline intraesophageal pressure.

Accompanying this rise in esophageal pressure is a severe pain in the chest that is most uncomfortable to the patient. At this point, 0.4 mg of atropine sulfate (in a syringe previously made ready) is given slowly intravenously. This brings prompt relief of the pain and a corresponding drop in intraesophageal pressure as recorded by the catheters in the midesophagus.

The paper speed is 1 mm per second during the Mecholyl test. Patients with history of asthma should be excluded from this portion of the test because of the potential danger of Mecholyl in creating bronchospasm.

When a patient with advanced achalasia lies on his back, excessive secretions retained in the dilated esophagus may cause coughing which in-

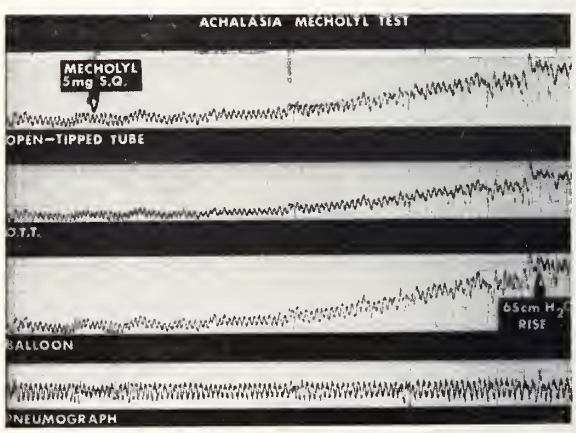


Figure 6.—Mecholyl® test in achalasia reveals rise in intraesophageal pressure of 65 cm of water. The tracing was taken in the mid-esophagus.

terferes with accurate intraluminal recording of pressure. The greatly dilated esophagus also may make passage of the catheter unit through the gastroesophageal sphincter into the stomach quite difficult or impossible. In such cases, however, the diagnosis of achalasia is seldom in doubt.

Treatment of achalasia includes pneumostatic dilation of the gastroesophageal sphincter under careful fluoroscopic control and the Heller operation, a myotomy of the proximal two-thirds of the lower sphincter.

Diffuse Spasm

Diffuse spasm of the esophagus, found in 22 patients in this study, is believed to be a functional disorder characterized by thoracic pain or dysphagia or both. In this condition, unlike achalasia, no evidence of myentric plexus degeneration has been reported.[5]

Barium study of the esophagus may be normal or may show nonprogressive simultaneous contractions. Because of the inconsistency of x-ray findings, esophageal motility studies are vital in helping to make this diagnosis with accuracy.

Diffuse esophageal spasm may be primary, with no apparent cause, or secondary to acid reflux found in hiatal hernia, scleroderma or a low pressure gastroesophageal sphincter. The swallowing contractions are of much greater than normal amplitude and length in diffuse spasm and are simultaneous (Figure 7). Double and occasionally even triple peaked waves may be seen following a single swallow.

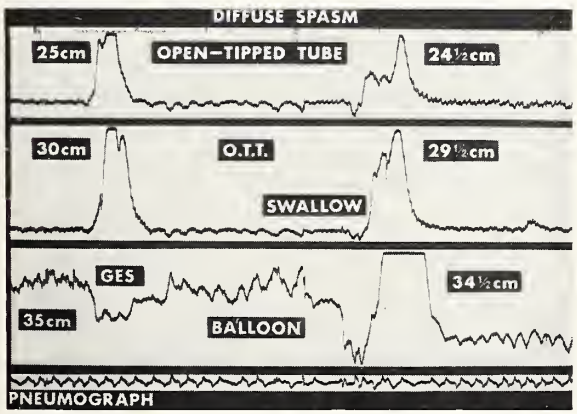


Figure 7.—Record of patient with diffuse spasm of the esophagus shows simultaneous swallowing waves of excessive amplitude and length. Note that unlike the reaction in patients with achalasia, the gastroesophageal sphincter relaxes with a swallow in this disorder.

Usually the disorder is confined to the lower one-half or lower one-third of the esophagus. The patient does not need to experience pain at the time of the test in order for the diagnosis to be made accurately by esophageal motility tracings. In this disorder, unlike achalasia, the lower esophageal sphincter does relax normally following a swallow.

The length of the gastroesophageal sphincter in this study averaged 4.1 cm in diffuse spasm as measured by the open tipped catheters. The mean pressure of the gastroesophageal sphincter above the mean fundic pressure of the stomach was 16.6 cm of water, as recorded by the open tipped tubes.

Conservative treatment has not been very effective in controlling the symptoms of this usually benign disorder. Rapid swallowing of solid food, of ice cold liquids or of other irritants should be avoided. Nitroglycerine or amyl nitrite will usually relieve the pain in the chest immediately, but only temporarily. Long-acting nitrites may be tried. Unlike smooth muscle spasm in other parts of the gastrointestinal tract, such as in the irritable bowel syndrome, diffuse esophageal spasm usually does not respond well to anticholinergic therapy.

Surgical treatment includes the long esophagomyotomy described by Ellis.[4] Since diffuse spasm of the esophagus is usually a benign and intermittent disorder, long myotomy should be reserved for patients who are losing weight or going downhill despite a good trial of conservative therapy.

Scleroderma

In scleroderma the esophagus is more frequently involved than other portions of the gastrointestinal tract. In a series of 727 cases of systemic scleroderma, Tuffanelli and Winklemann[12] reported 42 percent of the patients complained of symptoms referable to the esophagus. When scleroderma does involve the esophagus, progressively weak and simultaneous contractions are seen in esophageal motility tracings (Figure 8).

Nineteen of 88 patients in the present study were found to have scleroderma of the esophagus. This unusually high proportion probably reflects both the large number of patients with this disorder sent to a university medical center and frequent referral by the department of dermatology.

Motility changes in scleroderma have recently been well summarized by Saladin and coworkers.[9] Patients with scleroderma may have no esophageal

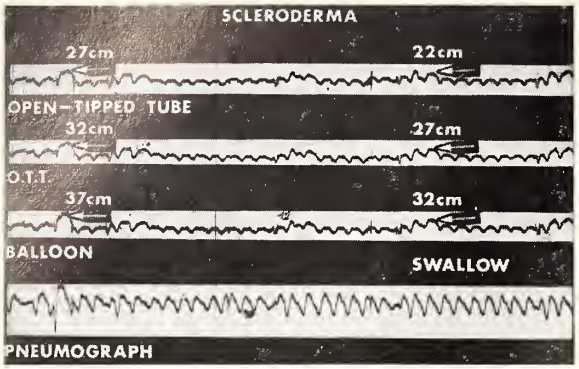


Figure 8.—Motility tracing of patient with scleroderma reveals simultaneous, weak swallowing responses similar to patients with achalasia. Mecholyl® gives no rise in intraesophageal pressure in scleroderma.

symptoms such as dysphagia, heartburn or painful swallowing, yet have abnormal motility tracings. Early changes in esophageal motility in scleroderma can be found long before abnormalities are reported on esophageal roentgen studies.

Tracings in advanced scleroderma are quite similar to those in advanced achalasia. However, although the resting pressure in the gastroesophageal sphincter in scleroderma is often less than normal, usually the lower sphincter does relax to some extent following a swallow. In achalasia there is no relaxation following the deglutition in the lower sphincter.

The length of the gastroesophageal sphincter averaged 3.4 cm in patients with scleroderma. The mean pressure of the gastroesophageal sphincter above mean fundic pressure of the stomach was 10.4 cm in scleroderma. The Mecholyl test, positive in achalasia, is negative in scleroderma. It is now believed that smooth muscle atrophy, rather than connective tissue replacement of smooth muscle, is the chief underlying pathological change in this disease.[11]

Esophageal motility abnormalities similar to those seen in scleroderma have been reported in dermatomyositis.[13] Similar changes on esophageal motility tracings have been found in patients with Raynaud's phenomenon alone, before any collagen disease is clinically evident.[10] Therefore, esophageal motility studies should be done on any patient with scleroderma, with or without swallowing symptoms, to help determine whether the smooth muscle of the esophagus has been involved in the course of the disease. To date, there is no known effective treatment for scleroderma.

Hiatal Hernia

Hiatal hernia was diagnosed in 13 patients in this study. Often this diagnosis is difficult to make on the basis of esophageal motility tracings. Several findings reported by Code and coworkers[2] should be present on the tracing to strongly suggest hiatal hernia. The most helpful criteria in making the diagnosis of hiatal hernia in the present study included:

- Increased length of the gastroesophageal junctional zone on the resting study.
- A pressure plateau in the junctional zone.
- A decrease in the amplitude of the normal respiratory excursion in a portion of the gastroesophageal zone.
- Two peaks of increased pressure in the elongated junctional zone, indicating separation of the diaphragm from the abnormally elevated gastroesophageal sphincter.

Motor dysfunction in the form of diffuse spasm or incoordination in the lower esophagus was often found associated with hiatal hernia. Similar findings were reported by Kelley.[8]

Hypertonic Esophagus

Hypertonic esophagus is a term used for patients with swallowing waves of increased amplitude and length but with normal peristalsis and no simultaneous contractions present. This disorder is probably closely related to diffuse spasm of the esophagus. The chief difference between the two is that, by definition, in diffuse spasm there should be some evidence of simultaneous contractions on the motility record to prove that spasm actually takes place, at least over a 5 cm portion of the esophagus.

Hypertonic esophagus was diagnosed in eight patients in this study. Treatment is similar to that outlined under conservative treatment of diffuse spasm.

Leiomyoma, Carcinoma and Benign Stricture

Roentgenographic and esophagoscopic examination are more definitive diagnostic procedures for these obstructive disorders. If the obstruction is large enough, of course, the balloon tipped motility unit will not pass down the esophagus beyond the point of obstruction. The maximum distance of passage of the unit from the incisor teeth then should be measured and recorded. Esophageal

motility tracings in the area immediately above the obstruction, no matter what the underlying disease may be, often show repetitive or other abnormal contractions following a single swallow, as if the esophagus were trying to pump the saliva beyond the obstruction. One patient, later proven to have carcinoma of the esophagus, showed swallowing waves on the motility test indistinguishable from those seen in achalasia. In addition, a moderate rise in intraesophageal pressure was seen in the Mecholyl test in this patient.

Low Pressure Gastroesophageal Sphincter

As measured by the open tipped catheter, in normal subjects the mean resting pressure of the gastroesophageal sphincter above mean fundic pressure in the stomach in this study was 12.2 cm of water. Three patients who complained of heartburn and other symptoms of reflux esophagitis had consistent pressure readings in the lower esophageal sphincter of 5 cm of water or less without other apparent disease such as scleroderma or hiatal hernia. It is believed these patients had a poor tonic contraction of circular smooth muscle fibers in the lower sphincter and that this accounted for their symptoms of acid reflux, especially noted when lying down. Mild secondary diffuse spasm and incoordination in swallowing responses in the lower esophagus, thought to be secondary to acid irritation, were seen in this group of patients.

Hypertensive Sphincter

Surprisingly the diagnosis of hypertensive sphincter, first suggested by Code in 1960,[3] was made in only one instance in the present study. According to Code, a resting pressure of over 40 cm of water in the gastroesophageal sphincter, as recorded by the open-tipped catheters, classifies the lower sphincter as hypertensive. Four percent of Code's 514 consecutive esophageal studies fell into this category.[3] This disorder is often associated with diffuse spasm of the lower esophagus. If symptoms are persistent and severe despite conservative treatment, myotomy of the hypertensive sphincter may greatly help the patient.

GENERIC AND TRADE NAME OF DRUG

Metacholine chloride—*Mecholyl®*

REFERENCES

1. Code, C. F., Creamer, B., Schlegel, J. F., Olsen, A. M., Donoghue, F. E., and Anderson, H. A.: An Atlas of Esophageal Motility in Health and Disease, Charles C Thomas, Springfield, Ill., 1958.

2. Code, C. F., Kelley, M. L. Jr., Schlegel, J. F., and Olsen, A. M.: Detection of Hiatal Hernia During Esophageal Motility Tests, Gastroenterology, 43:521, 1962.

3. Code, C. F., Schlegel, J. F., Kelley, M. L. Jr., Olsen, A. M., and Ellis, F. H. Jr.: Hypertensive gastroesophageal sphincter, Proceedings Staff Meet. Mayo Clinic, 35:391, 1960.

4. Ellis, F. H. Jr., Code, C. F., and Olsen, A. M.: Long esophagomyotomy for diffuse spasm of the esophagus and hypertensive gastroesophageal sphincter, Surgery, 48:155, 1960.

5. Fleshler, Bertram: Diffuse esophageal spasm, Gastroenterology, 52:559, 1967.

6. Fyke, F. E. Jr., Code, C. F., and Schlegel, J. F.: The gastroesophageal sphincter in healthy human beings, Gastroenterologia, 86:135, 1956.

7. Kelley, M. L. Jr., Wilbur, D. L. III, Schlegel, J. F., and Code, C. F.: Deglutitive responses in the gastroesophageal sphincter of healthy human beings, J. Appl. Physiol., 15:483, 1960.

8. Kelley, M. L. Jr.: Deglutitive pressure responses in the gastroesophageal sphincters of symptomatic hiatal hernia patients, Am. J. Diges. Dis., 10:582, 1965.

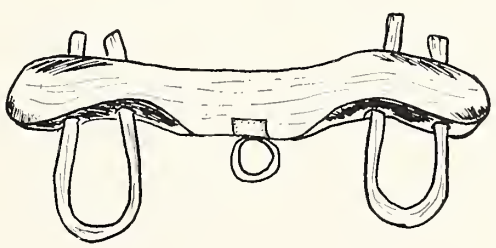
9. Saladin, T. A., French, A. B., Zarofonetis, C. J. D., and Pollard, H. M.: Esophageal motor abnormalities in scleroderma and related diseases, Am. J. Diges. Dis., 11: 522, 1966.

10. Stevens, M. B., Hookman, P., Siegel, C. I., Esterly, J. R., Shulman, L. E., and Hendrix, T. R.: Aperistalsis of the esophagus in patients with connective tissue disorders and Raynaud's phenomenon, New Eng. J. Med., 270: 1218, 1964.

11. Treacy, W. L., Baggenstoss, A. H., Slocumb, C. H., and Code, C. F.: Scleroderma of the esophagus: A correlation of histologic and physiologic findings, Ann. Int. Med., 59:351, 1963.

12. Tuffanelli, D. L., and Winklemann, R. K.: Systemic scleroderma: Clinical study of 727 cases, Arch. Derm., 84:359, 1961.

13. Wilbur, D. L. III, Pollard, H. M., and Saladin, T. A.: Esophageal motility tests in the diagnosis of esophageal disease, Univ. Mich. Med. Cent. J., 32:229, 1966.



Carcinoma of the Thyroid Gland

A 15-Year Survey in Private Hospitals in Sacramento

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■ *All cases of carcinoma of the thyroid gland diagnosed at two large hospitals in Sacramento during the 15 year period 1951-1965 were studied. Of the 232 cases diagnosed, 179 or 77.2 percent were papillary carcinoma. It was possible to trace 94 percent of all the patients, with a median follow-up of 6.5 years, and no deaths due to papillary carcinoma of the thyroid were found. The extent of operation did not appear to influence the course of papillary carcinoma of the thyroid.*

DURING THE 15 YEAR period of the survey here reported, the diagnosis and treatment of carcinoma of the thyroid gland have been widely discussed but as yet there is a striking lack of uniform opinion regarding the ideal management, particularly of thyroid papillary carcinoma. In general, the tendency of a number of investigators has been to recommend more radical operation,[2,7,12] and this is reinforced by reports from some centers showing a significantly high mortality rate from carcinoma of the thyroid gland, including papillary carcinoma.[6,7,8,13,16] The more radical approach has been supported by an increasing recognition of multicentric origin of thyroid carcinoma,[1] of the occurrence of bilateral disease,[7,8,10,11] and of the problem of "stump recurrences."[1] In addition, evidence of metaplasia or transition from a less malignant to a more malignant form of the disease with the passage of years has led to a more aggressive surgical position.[6,8,11,16]

The present study was begun in part because of comments by local pathologists that they had not performed an autopsy in Sacramento in a case of papillary carcinoma of the thyroid.

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Materials and Methods

This survey is based on a follow-up of all the cases of carcinoma of the thyroid treated at two large private hospitals in Sacramento. To put the matter in proper perspective, it should be noted that the population of Sacramento County is now in excess of 600,000, and the hospitals in the city serve, to some extent, an equal number of people from outlying areas. During the period of this study, there were two major hospitals in Sacramento which have consistently expanded over the years. The present bed capacity of Sutter Community Hospitals is 541, and of the Mercy Hospital is 311, a total of 852. In recent years, two or three additional hospitals have begun operation in the Sacramento area, but these were not included in this review.

The number of hospital admissions and the number of operations performed in the Sutter and Mercy Hospitals during the period under review are shown in Chart 1. The admission rate for the Sutter Hospitals has increased from 14,218 in 1950 to 26,530 in 1965. Similarly, the Mercy Hospital has increased its admission rate from 8,823 in 1951 to 19,196 in 1965. The total num-

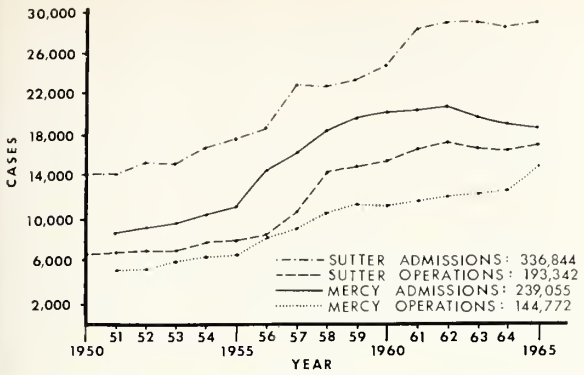


Chart 1.—Hospital admissions and operations, Sutter and Mercy Hospitals, 1950-1965.

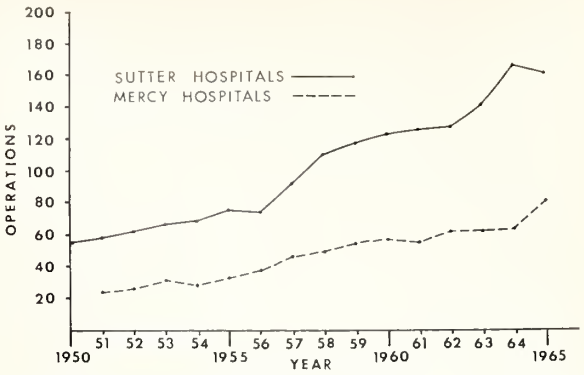


Chart 2.—Thyroid operations, all types, Sutter and Mercy Hospitals, 1950-65.

ber of admissions to the Sutter Hospitals over this 15 year period is 336,844 and to the Mercy Hospital is 239,055, for a total of 575,899 hospital admissions during this time.

The number of surgical procedures at these hospitals has increased (as shown in Chart 1). During this period the total number of operations performed at the Sutter Hospitals was 193,342, and at the Mercy Hospital 144,772, and the total was 338,114. Thyroid gland operations of all types performed during this period have increased (Chart 2). The number of thyroid gland operations of all kinds at the Sutter Hospitals was 1,618 and the number at the Mercy Hospital was 704, a total of 2,322.

Carcinoma of the thyroid gland was found in 229 (10 percent) of this total of 2,322 thyroid operations. It is this group of 229 cases, plus three cases in which carcinoma was found at autopsy—232 cases in all — that forms the basis for this report. The incidence of diagnosis of carcinoma of the thyroid has increased over the years as indicated in Chart 3.

Comparison of Charts 2 and 3 shows that while the number of thyroid operations has increased, the incidence of thyroid carcinoma has fluctuated rather widely, from a low of 4.1 percent in 1953 to a high of 15.2 percent in 1960, with an average incidence of slightly less than 10 percent. There has not been any increase in the incidence of carcinoma of the thyroid gland in patients who have had a thyroid operation during the 15 year period of this study. The year to year variation most likely represents variation in the histologic interpretation of the material by the various pathologists who examined the specimens.

There are a number of ways of classifying malignant tumors of the thyroid gland, and it is not the purpose of this report to argue for any particular scheme of classification, nor to challenge the criteria for the diagnosis of the various carcinomas reported. The classification used in this report is one that is generally accepted, is utilized by our local pathologists, and seems to fit well with the material being studied. The types of carcinomas found are shown in Chart 4.

Of the 232 cases, 179 or 77.2 percent were papillary carcinoma, 12 or 5.2 percent were fol-

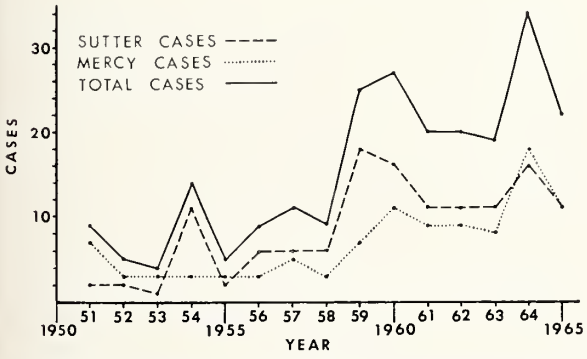


Chart 3.—Number of cases of thyroid carcinoma at Sutter and Mercy Hospitals, 1951-1965.

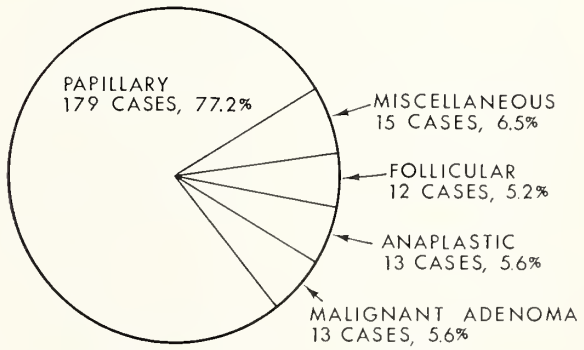


Chart 4.—Carcinoma of the thyroid, 232 cases, 1951-1965.

licular carcinoma, and 13 or 5.6 percent were anaplastic carcinoma. In addition there were 13 cases (5.6 percent) of malignant adenoma and 15 (6.5 percent) miscellaneous carcinomas. The miscellaneous tumors included ten cases of sclerosing carcinoma, two cases of spindle-cell carcinoma, two cases of Hurthle cell carcinoma, and one case of clear-cell carcinoma. The age distribution of the patients reported was 6 to 84 years, with an average age at the time of initial treatment of 38.5 years. There were 172 female patients and 60 male patients, roughly a 3 to 1 ratio.

Method of Follow-up

The record rooms of the two hospitals and the pathology departments provided the initial listing of patients eligible for the study. Follow-up information was obtained from the tumor registries at the hospitals, as well as by direct personal contact by the authors with the surgeons who had provided the initial treatment or with the family physicians. In many cases, direct contact was made with the patient. Follow-up was considered complete only if the patient's condition could be identified up to and including 1967. With these criteria, the overall complete follow-up rate was 94 percent. Nine patients on whom follow-up information was available for a time and then were lost to follow-up were considered "partially traced."

The methods of treatment of the 232 patients in the series were as follows:

Less than one lobe removed	8
One lobe removed	80
Bilateral thyroid operation	133
Biopsy only	8
Found at autopsy only	3
Total	232

No attempt was made in the present study to differentiate among a bilateral subtotal thyroidectomy, a unilateral total lobectomy plus contralateral subtotal lobectomy and a bilateral total thyroidectomy, primarily because of difficulty in precise interpretation of the various operative reports. There were 106 patients in whom lymph nodes were examined, including 95 node dissections, eight biopsy procedures, and three cases in which carcinoma was detected at autopsy. Of these 106 patients, 88 had nodes positive for carcinoma. Because of the great variation in operative procedures, no attempt is made in this study to differentiate various types of lymph node resection or to determine the follow-up results based on various types of lymph node resections.

Findings

The results of attempted follow-up of these 232 cases were as follows:

	Papillary	*Follicular*	*Anaplastic*	*Malig. adenoma*	*Misc.*	*Total*
Living and well	157	9		12	13	191
Dead of other causes	9		1			10
Dead—surgical mortality	2					2
Dead of thyroid carcinoma			10		1	11
Found at autopsy only	1	1			1	3
Partially followed	5	2	1	1		9
Untraced	5		1			6
Total	179	12	13	13	15	232

The nine patients with papillary carcinoma of the thyroid known to have died of other causes had the following causes of death: Carcinoma of the ovary, coronary occlusion, leiomyosarcoma of the esophagus, uremia, cerebral vascular accident, suicide, acute leukemia, myasthenia gravis, and injuries received in an automobile accident. There were two patients who died of surgical complications. One of these died during operation with tachycardia, hyperthermia, and cardiac arrest, of suspected masked hyperthyroidism, and one patient died postoperatively from hemorrhage adjacent to tracheostomy.

Of the 13 patients with anaplastic carcinoma of the thyroid gland, ten died of the disease (all within a year of operation), one died of other causes, one is untraced and one has been only partially traced. Of the 12 with follicular carcinoma, nine are living and well, two have been only partially traced and in one the lesion was not found until autopsy.

There has been an accurate and complete follow-up up to and including 1967 on 217, or 94 percent, of the 232 patients, with the follow-up periods ranging from a minimum of two years to a maximum of 16 years, and a median of 6.5 years for those surviving. Of the total of 232, six are completely untraced, and nine patients have been partially traced for a period ranging from one to eleven years (median six years) and none of these patients are known to have died of thyroid carcinoma. For the purposes of completeness, a specific search of death records at the Sacramento County Hospital was made, and it was found that

none of the untraced or partially traced patients in this series had died there with carcinoma of the thyroid gland, either as a cause of death or as an accessory finding at death.

Certain aspects of follow-up were intentionally deleted. It is known, for example, that a considerable number of this group are receiving thyroid hormone by mouth, particularly those operated on in recent years, but information about the amount and duration of treatment is not accurate enough to justify reporting. A few patients received radioactive iodine, either to ablate remaining thyroid tissue or as treatment for suspected metastasis. It is also known that four patients are currently under observation or treatment for possible distant metastatic lesions. In only one case was there a serious suggestion of stump recurrence. The patient was a girl who at age 8 had a papillary carcinoma on the right side and at age 16 had a papillary carcinoma removed from the left side.

Discussion

The most striking finding of this survey is that there are no proven deaths due to papillary carcinoma of the thyroid gland in the 94 percent of the patients followed. This is in decided contrast to the reports of Frazell and Foote,[6] Silliphant,[13] Tollefsen,[16] and Hirabayashi and Lindsay.[7] The report of Hirabayashi and Lindsay, for example, shows an 11 percent mortality rate from papillary carcinoma of the thyroid gland in a series extending over 40 years. The series reported in this paper does not conform to the findings of a high incidence (12 percent) of multicentric tumors, as reported by Black,[1] nor does it indicate a high incidence of bilateral dissemination of the tumor, reported by Hirabayashi and Lindsay at 19 percent, and up to 88 percent by Ibanez and coworkers[8] at the M. D. Anderson Hospital in Texas. In the present series the incidence of recurrent or persistent tumor or "stump recurrence" was lower than the 5 percent reported by Tollefsen[15] and the 6 percent by Black.[2] It is of interest also, that, in the present series none of the patients who were seen first with papillary carcinoma was later found to have died of anaplastic carcinoma, and none of the patients who died of anaplastic carcinoma was shown to have started out with a papillary carcinoma. The concept of transition of malignant change to more undifferentiated tumors as suggested by a number of investigators, including Frazell and Foote,[6] Ibanez,[8] and Russell[11] from the M. D. Anderson Hospital, and Tollefsen,[16] from the Memorial Hospital in New York, was not supported in the present study.

There are at least two limitations in this study which require comment, namely, the number of cases and the length of follow-up. The present series of 232 cases, including 179 cases of papillary carcinoma, is of the same order of magnitude as the series of 328 cases of papillary carcinoma from the Mayo Clinic reported by Black[1] and the series of 390 cases of all types recorded by Hirabayashi and Lindsay.[7] The 700 cases reviewed by Tollefsen[16] from the Memorial Hospital and James Ewing Hospital in New York are not comparable because they include patients previously treated elsewhere, patients with very large tumors and patients with vocal cord paralysis or other evidence of inoperability.

As was stated above, the follow-up period of the present series extends from a minimum of two years to a maximum of 16 years, with a median of 6.5 years for all surviving patients. It has been repeatedly pointed out that even longer follow-up is necessary for proper evaluation of mortality rates. However, Frazell and Foote[6] noted that, of 47 patients with papillary carcinoma in their series who died, 27 were dead within the first five years. Likewise in Tollefsen's series,[16] the median survival time for all patients was five years, and if the patient was never cancer-free, the median survival time was only 14 months. If there was a cancer-free interval following operation, the median survival time was nine years, a figure not out of line with the present report.

Using the foregoing figures for comparison, one should expect a significant number of deaths in this report. The absence of death due to papillary carcinoma reported in the present series gives grounds for several possible interpretations. It is possible that certain of the carcinomas in this report are similar to the "occult carcinomas" described by Woolner,[17] with a zero death rate, or to the "laboratory carcinomas" mentioned by Frazell and Foote.[6] The findings of the present series are most in line with those of Crile,[5] who described 140 patients with papillary carcinoma of the thyroid gland followed by him over a period of five to twenty-five years, with the survival rate in women with the disease equal to the survival rate in the rest of the population. Crile excluded those cases of papillary carcinoma in which there

were any areas of undifferentiated carcinoma, a distinction that was not made in the present study.

Another remarkable finding in the present series is that metastatic involvement of the lymph nodes was shown in 95 of the 106 cases in which lymph nodes were available for study. One might speculate that the surgeons involved are particularly skillful in grossly detecting suspicious lymph nodes, but since it is well known that it is difficult to detect involvement of nodes by gross examination, it seems probable that there is residual carcinoma remaining in the lymph nodes of at least some of these patients. One must presume either that papillary carcinoma of the thyroid has a very low degree of malignancy or that other factors such as thyroid supplementation are suppressing the spread of the tumor for extended periods.

If the findings of other series are carried to their logical conclusions, operations would be increasingly radical in terms of resection of thyroid and lymph node tissue. There is considerable support in the literature for unilateral thyroid lobectomy on the side of the lesion plus subtotal resection of the opposite lobe, but bilateral total thyroidectomy is only recommended by a few observers, and many of the operations they carry out are not truly total thyroidectomy. In fact, Block[3] has shown that 32 percent of his patients have functioning thyroid tissue remaining after presumed bilateral total operation. The hazard of damage to the parathyroid glands is well known, and the incidence of postoperative hypoparathyroid tetany, ranging from 50 percent permanent tetany as reported by Black,[1] down to 12.8 percent permanent tetany as reported by Clark,[4] must force even skilled surgeons to seriously consider the risks.

There has also been a considerable tendency in recent years toward more radical resection of regional lymph nodes. No support can be gained for this in the present series, and there appears to be at least some theoretical reason to question the logic of routinely extending lymph node dissection to the jugular nodes, since it has been shown by injection studies in human patients at operation that the lymphatic drainage of the thyroid gland goes as much to the lymphatic chain in the tracheal wall itself and to the nodes in the tracheoesophageal groove, mediastinum and thymus as it does to the nodes encompassed in a standard or modified radical neck dissection.[9,14] The results of this survey imply that radical operation is not the *sine qua non* for prolonged survival with papillary carcinoma of the thyroid gland, and that any operation, of whatever extent, is unsatisfactory for anaplastic carcinoma.

Summary and Conclusions

- The reported cases represent a 15-year survey of all cases of thyroid carcinoma diagnosed in two large private hospitals in Sacramento.
- Two hundred and thirty-two cases of carcinoma of the thyroid are reported, including 179 of papillary carcinoma, 12 of follicular carcinoma, 13 of anaplastic carcinoma, 13 of malignant adenoma, and 15 of miscellaneous malignant lesions.
- In follow-up studies 94 percent of the entire group was accounted for over a 15-year period.
- There are no deaths due to the disease in the group of 179 cases of papillary carcinoma of the thyroid thus followed.
- Anaplastic carcinoma of the thyroid gland is uniformly and rapidly lethal regardless of treatment.
- The extent of the operation does not appear to significantly affect the course of papillary carcinoma of the thyroid gland.
- Other factors, such as the use of thyroid hormone postoperatively, may be responsible for the prolonged survival of patients with papillary carcinoma.
- There is a conspicuous lack of clinical findings in this series to support the concept of multicentric tumors, bilateral involvement of the gland, intraglandular spread and transition to more malignant tumors.

REFERENCES

1. Black, R M., Kirk, T. A., and Woolner, L. B.: Multicentricity of papillary adenocarcinoma of the thyroid: influence on treatment, J. Clinical Endocrinology and Metabolism, 20:130, Jan. 1960.

2. Black, R. M., YaDeau, R. E., Woolner, L. B.: Surgical treatment of thyroidal carcinomas, Arch. Surg., 88: 610, Apr. 1964.

3. Block, M. A., Horn, R. C., and Brush, B. E.: The place of total thyroidectomy in surgery for thyroid carcinoma, Arch. Surg., 81:236, Aug. 1960.

4. Clark, R. L., Ibanez, M. L., and White, E. C.: What constitutes an adequate operation for carcinoma of the thyroid?, Arch. Surg., 92:23, Jan. 1966.

5. Crile, G., Jr.: Survival of patients with papillary carcinoma of the thyroid after conservative operations, Am. J. Surg., 108:862, Dec. 1964.

6. Frazell, E. L., and Foote, F. W.: Papillary cancer of the thyroid: a review of 25 years of experience, Cancer, 11:895, Sept. 1958.

7. Hirabayashi, R. N., and Lindsay, S.: Carcinoma of the thyroid gland: A statistical study of 390 patients, P. Clinical Endocrinology and Metabolism, 21:1596, Dec. 1961.

8. Ibanez, M. L., Russell, W. O., Albores-Saavedra, J., Lampertico, P., White, E. C., and Clark, R. L.: Thyroid carcinoma—biologic behavior and mortality: postmortem findings in 42 cases including 27 in which the disease was fatal, Cancer, 19:1039, Aug. 1966.

9. Richardson, P. J., and Taylor, S.: A study of the lymphatic drainage of the human thyroid, British J. Surg., 51:73, Jan. 1964.

10. Rose, R. G., Kelsey, M. P., Russell, W. O., Ibanez, M. L., White, E. C., and Clark, R. L.: Follow-up study of thyroid cancer treated by unilateral lobectomy, Am. J. Surg., 106:494, Sept. 1963.

11. Russell, W. O., Ibanez, M. L., Clark, R. L., and White, E. C.: Thyroid carcinoma: classification, intraglandular dissemination, and clinicopathologic study based upon whole organ sections of 80 glands, Cancer, 16:1425, Nov. 1963.

12. Sedgewick, C. E., and Konvolinka, C. W.: Management of carcinoma of the thyroid, Surg. Clin. N.A., 47: 607-612, June 1967.

13. Silliphant, W. M., Klinck, G. H., and Levitin, M. S.: Thyroid carcinoma and death: a clinicopathological study of 193 autopsies, Cancer, 17:513, Apr. 1964.

14. Taylor, S.: Surgical treatment of carcinoma of the thyroid, Brit. J. Surg., 52:740, Oct. 1965.

15. Tollefsen, H. R., and DeCosse, J. J.: Papillary carcinoma of the thyroid: recurrence in the thyroid gland after initial surgical procedure, Am. J. Surg., 106:728, Nov. 1963.

16. Tollefsen, H. R., DeCosse, J. J., and Hutter, R. V. P.: Papillary carcinoma of the thyroid: a clinical and pathological study of 70 fatal cases, Cancer, 17:1035, Aug. 1964.

17. Woolner, L. B., Lemmon, M. L., Beahrs, O., Black, M., and Keating, F. R.: Occult papillary carcinoma of the thyroid gland: a study of 140 cases observed in a 30 year period, J. Clinical Endocrinology and Metabolism, 20:89, Jan. 1960.



Individual Normal Laboratory Values

Preliminary Observations

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■ *A brief and preliminary outline is given describing a consecutive and continuing study of laboratory blood values of only 12 of 48 "normal healthy" subjects with only a few values given. The major emphasis is that of obtaining blood from each subject over a 12-week period to be repeated annually in order to determine individual values and in obtaining a chemical identification of each subject with the anticipation that more information will be available concerning the meaning and limiting parameters of "normal" biologic values. Such a study is made available through the application of modern advances in automation and the wide use of computers. It seems likely that some disorders can be discovered before clinically apparent, with the hope that consequent preventive measures and therapy may be more effective.*

The few values presented represent only a small part of those yet to be obtained. Much more work is needed in this study of normal values whose parameters must be further defined.

TO UNDERSTAND THE MEANING and application of "normal values" it is essential to discuss, however briefly, statistical terms and concepts so frequently employed in communicating results. After measuring a certain characteristic, for example the level of glucose in blood, we consider such features as the number of determinations made, the number of persons from whom the specimens were obtained, age, sex and the state of nutrition. In general we add up all the individual observations and divide by the number of determinations and obtain a value commonly called average.

Strictly speaking, there are three values which could be obtained to represent the entire group of determinations, each of which has its own special use. These values are the mean, the mode and the median.

The mean value is what is commonly called the average value and is determined by dividing the sum of the individual observations by the number of observations, often called the sample. The mode is determined by first categorizing the values. For example, with regard to blood glucose, categories or classes of values might be established as 50 to 59 mg, 60 to 69 mg per 100 ml, and so on. One then plots the number of determinations that falls in each of these categories or classes and that class which has the largest number of values is called the mode.

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The median is that value above which half of the values fall and below which half of the values fall when listed in order of magnitude. Again using blood glucose as an example, let us suppose that we have seven values, 50, 65, 80, 85, 90, 100 and 120 mg per 100 ml. The central value, 85 mg, is the median value as it divides those listed equally. In an even number of observations an average of the two middle observations would be the median. In a symmetrical continuous distribution noted in a true bell-shaped curve, the mode, median and mean are coincident; this does not apply in a skewed distribution.

Now, if we have studied a sufficiently large enough group of individuals, that is if we have an adequate sample (usually normal but not necessarily so), and if they are healthy adults in general of the same age group and sex, and we plot our individual observations in the form of a histogram or bar graph, and then fit a curve to this, we end up with what is called a normal frequency distribution or Gaussian curve. Expressed as a bell-shaped curve, the values are close to or actually bilaterally symmetrical. If our sample was adequate in all respects we would find that the mean, the mode and the median would all practically coincide. Since in further statistical applications a numerical value is needed, of the three means of expressing average, the mean is the one usually chosen to express the group.

Having obtained the mean of the set of observations made, it is useful and desirable to have some way of deciding whether or not a given value which is different from this mean is really abnormally high or abnormally low so that we can attach meaning to it. Put another way, at what point do we have to begin worrying about a value which differs from the mean? A practice more common in the past than at present was to express the mean plus the highest and the lowest observed values as the range. This method, still useful, sets unduly broad limits of range and leads to failure to detect abnormal values closer to the mean value. It is preferable to calculate limits called standard deviation (SD).

Standard deviation, by definition, is the square root of the average of the squared deviations of the individual measurements from their mean (M). Just how this mathematical expression proves useful in considering the possible significance of a single measurement may be explained as follows:

• Utilizing blood glucose measurements as an example, suppose that after measuring the blood glucose level of 100 clinically healthy people we calculated the mean was 100 mg per 100 ml and the SD was + or — 10 mg.

• Suppose that next we actually plotted on a graph the individual measurement and then drew in on the graph the position of the mean value which was 100 mg and to either side of the mean the limits of one, two and three standard deviations (SD's) which would be respectively on the positive side 110, 120 and 130 mg and on the negative side 90, 80 and 70 mg. If we then counted up the actual individual observations which fall between the mean and these successive limits of plus or minus 1, 2 and 3 SD's, we would learn something as follows: About 68 of the 100 observations would fall between minus 1 and plus 1 SD; about 95 of the 100 observations would fall in the limits set up by minus 2 and plus 2 SD's and about 99 of the 100 values would fall in the limits set up by 3 SD's to either side of the mean.

• How can we use such information to decide whether a single given value obtained subsequently on another person is within normal limits, high or low? Commonly, 2 SD's are said to represent normal limits but exactly what is meant by this? We have said that 95 of the 100 values fell within the limits of 2 SD's. Five of the values fell outside these limits. Therefore, the chances are only 5 of 100 or 1 in 20 that a value falling outside the limits of 2 SD's is normal or, putting it the other way, the chances are 19 out of 20 that such a value is abnormal.

• For these reasons, it is customary in trying to assess the significance of an individual value, as compared with the group, to set limits of 2 SD's; in some circumstances it is considered essential to be more stringent and in such instances limits of 3 SD's are set. If a value is greater than 2 SD's away from the mean, on either the high or the low side, the chances are only 1 in 20 that it is a normal value and 19 out of 20 that it is abnormal; if a given value is more than 3 SD's away from the mean, the chances are less than 1 in 100 that it is normal and conversely better than 99 in 100 that it is abnormal.

• Returning now to our example of blood glucose with a mean value of 100 mg and a SD of plus or minus 10 mg, it is possible to state that

if we receive a value of 132 mg per 100 ml, the chances are greater than 99 out of 100 that this is high; or, if we obtain a value of 66 mg/100 ml, the chances are again better than 99 out of 100 that this value is low.

- It must always be kept in mind that the original observations on which the statistical values are based must be accurate, that the method used to obtain them must be a reliable one and that the sample on which the calculations are based was sufficiently large. The greater the number of observations, the more reliable the statistical values.
- The coefficient of variation (CV) expressed in percent gives the variability or variance among the several values obtained and is determined by dividing the mean into the standard deviation, times one hundred. The closer the CV approaches zero, the more precise is the value obtained. Well defined, accurate and precise techniques are necessary and give a small "CV"—a direct guide to precision. The CV here allows value comparison between different procedures, whereas such comparison cannot be made on unit measurement (mg, gm, units and the like). Technical CV which must be distinguished from interpersonal and intrapersonal variation will not be discussed here.

Observations

Clinicians and pathologists realize that the concept of "normal values" is a distinctively changing one. The differences of normal values with age, sex and analytical technique are well known. It is customary for laboratories to establish their own specific normal values for a given healthy population in order to allow reliance on procedures performed in the laboratory, with values out of the normal range usually considered significant and possibly related to the patient's disease. It has been established by Williams,[1] and emphasized by others, that the population range of normal is greater than a group range of normal which is in turn greater than an individual range of normal. It has been shown that each individual will have his own physiologic range which may be definitely abnormal for another of the same age and sex. In order to establish specific ranges for the individual, identifying him in a concept of chemical individuality, it is necessary to perform repeated determinations in a series of tests over a period of time.

The usefulness of regular testing has been pointed out by Perry, Williams and Kupfer[2] in the testing program for physicians carried out regularly at the annual meeting of the American Medical Association. This group stated: "The repetition of selected tests year after year should permit the physician to recognize the individual's normal range. A drift away from this range should serve to warn the physician of a developing dysfunction long before the process becomes irreversible and clinical disease is manifest."

The distinction between accuracy and precision must be made. Accuracy may be defined as closeness to the true value, whereas precision applies to the agreement of repeated measurements among themselves — that is, minimal variation in results when determination is made repeatedly. A given group of values may have excellent precision but if done incorrectly there will be no accuracy. A good example is the Folin-We method of determining blood "glucose" which may be quite precise yet inaccurate.

No attempt will be made to review the many articles found in the literature on normal values.

Material and Methods

Stimulated by the work of Williams,[1] six hospitals in the United States have engaged in a Nor-

TABLE 1.—*Presented is an analysis of the mean (M), one standard deviation (SD) and coefficient of variation (CV) of a 45 year old female. Biologic values are expressed per 100 ml. Donation of one pint of blood in February 1965 produced the hemoglobin and hematocrit variances noted when compared with those of 1966 and 1967. Most values are relatively close to one another over the three-year period.*

		1965	1966	1967
Glucose mg	M	83	78	89
	1SD	8	8	5.1
	CV%	9.6	10.1	5.7
Urea Nitrogen mg	M	16	16	16
	1SD	4.3	2.8	3.2
	CV%	27	17	20
Uric Acid mg	M	4.6	5.1	5.1
	1SD	0.36	0.14	0.71
	CV%	7.8	2.7	14
Cholesterol mg	M	214	224	221
	1SD	14.6	9.7	12.9
	CV%	6.8	4.3	5.8
Oxalacetic Transaminase (Karmen Units)	M	15	11	10
	1SD	2.9	2.3	2.8
	CV%	19	21	28
Hemoglobin gm	M	12.8	13.7	13.3
	1SD	0.79	0.49	0.45
	CV%	6.1	3.6	3.4
Hematocrit mm	M	41	43	41
	1SD	5.16	1.2	1.7
	CV%	12.5	2.8	4.2

mal Laboratory Test Profile study with periodic and repetitive studies of small groups of individuals. The Sutter Community Hospitals has been engaged in this study of normal values in cooperation with Williams and his group at the National Institutes of Health. We have completed the third year of this study (1967) which includes weekly analysis of blood obtained from 12 "normal" persons who are healthy hospital employees (six men and six women, nurses, aides, technologists and porters) each week for 12 weeks, with four groups (a total of 48 individuals) studied each year.

The hospital employees were chosen by personal interview after evaluating their completed detailed questionnaires and information from their private physicians concerning history and physical findings. Excluded were those with any persistent symptom or evidence of cardiopulmonary, hepatic, renal or other systemic disease. No attempt was made to alter the individual and usual diet. Annual reviews of health and physical condition were made before starting a 12-week period of testing. Information was exchanged with the private physician and correlated with the values obtained. All specimens were obtained in a fasting state after arrival of the subject at the hospital for the regular work period. The few personnel on medication were those taking estrogens, occasional aspirin and one on colchicine (note Table 2, uric acid). At present the first group is being studied for the fourth year in a row, with over 52,000 tests completed by the end of 1967. The study is planned to extend for five years. It is quite evident that a vast amount of data will become available after computer statistical analysis.

TABLE 2.—*The mean (M), standard deviation (SD) and coefficient of variation (CV) are given in a 56 year old male over a three-year period, as a result of 12 weekly similar determinations each year. Biologic values are expressed per 100 ml. Here also most values are close to one another from year to year. Note the high uric acid which was not associated with symptoms of gout until September of 1967.*

		1965	1966	1967
Glucose	M	86	82	93
mg	1SD	5	6.2	9.3
	CV%	5.8	7.5	10
Urea Nitrogen	M	16	15	16
mg	1SD	2.1	2.2	1.2
	CV%	13	15	7.5
Uric Acid	M	9.7	8.8	10.1
mg	1SD	0.46	0.22	1.04
	CV%	4.7	2.2	10.3
Cholesterol	M	247	240	248
mg	1SD	7.0	10.7	10.9
	CV%	2.8	4.5	4.4
Oxalacetic	M	29	20	25
Transaminase	1SD	3.9	2.7	4.4
(Karmen Units)	CV%	13	13.5	17.5
Hemoglobin	M	13.9	14.0	14.7
gm	1SD	0.38	0.42	0.95
	CV%	2.7	3.0	6.5
Hematocrit	M	45	44	45
mm	1SD	1.0	1.4	1.7
	CV%	2.2	3.2	3.8

Automated equipment consisted of five double channeled AutoAnalyzers for the chemistry procedures, Coulter counters for the erythrocyte and leukocyte counts and a Beckman Analytrol for paper electrophoresis. Such equipment allows, with careful quality control, a relatively narrow range of reproducibility and precision. As in any good quality control program, such tests can be performed accurately with adequate controls and standards. The tests performed on these 48 persons at Sutter Community Hospitals consist of blood glucose, blood urea nitrogen, uric acid, cholesterol, glutamic oxalacetic transaminase (Karmen units), alkaline phosphatase (Babson-Reed units), total protein, albumin and globulin, calcium, magnesium, serum protein electrophoresis with evaluation of alpha, beta and gamma globulins, as well as albumin, total white count, hematocrit, hemoglobin, red cell count and differential. All of the values were done in duplicate with tabulation of all values obtained in arriving at mean and standard deviation.

Information obtained in the study is being processed by computers at the National Institutes of Health with anticipation that much information will become available during the five years of study. The values given in the figures and tables below were obtained not by these computers but by hand electrical calculators.

Expected data to be obtained may answer the following questions: Is there a relationship between single or several values and age, sex or the development of disease? Is there possible variance with season, with geography (in relationship to other cooperative groups in the United States)? Why do some persons have a narrower variance of a given value then do others? Why do some persons have a narrower interpersonal variance in one year than in another? Will changes in some blood values be of greater help in predicting subclinical or overt disease?

The observations presented in this brief paper are only a few of those which apply to 12 individuals of the first group obtained over 12 successive

weeks each year in January, February and March of 1965, 1966 and 1967.

Results

Chart 1 is a bar-graph presentation of uric acid values obtained (mean and one standard deviation) from 12 individuals. Note that one man 59 years of age (M 59) was available only in 1965 and 1966 (died in October 1967) and that M 35 was available only in 1965 for this study. Note that each individual maintains a close mean value and one standard deviation over a three-year period, quite characteristic of most values obtained. The individual M 56 in Chart 1 was without any symptoms of gout until September of 1967. This feature suggests that a persistent elevation of serum uric acid should alert the clinician to the possibility of gout developing in his patient.

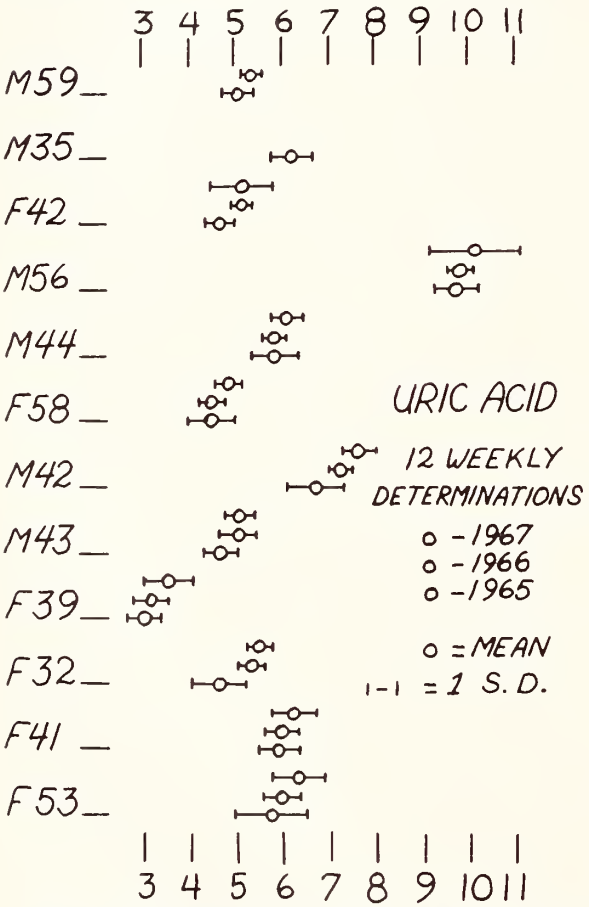


Chart 1.—Uric acid values are given stating the mean and one standard deviation of 12 successive weekly determinations each year over a three-year period. In groups of 3 the values for each subject represent from bottom to top the years 1965, 1966 and 1967. The left column identifies each subject by sex and age. Subjects M59 and M35 did not complete the three-year study. Values are given in mg per 100 ml.

Those individuals in our study with mild obesity had uniformly elevated values for blood glucose and cholesterol.

Chart 1 shows a "clustering" of uric acid values which may have some practical value if in subsequent years such values for one subject shift beyond two or three standard deviations. We may ask why does one subject maintain a narrow range (SD) and others do not? This feature was more evident in some of the other values obtained, not illustrated here. Would this suggest a tight and more restricted metabolism of uric acid, urea, glucose and the like?

In Chart 2 we see the mean values and standard deviations of 11 blood substances examined from a woman 42 years of age with a group mean of 1965 for comparison. The values of each of the other 11 persons in this group can be outlined in a similar manner, with each having a distinctive and non-identical pattern.

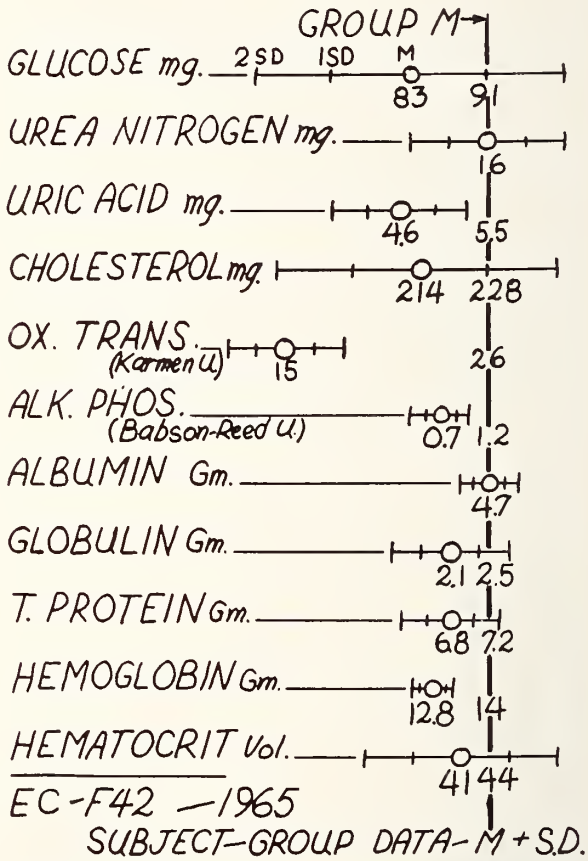


Chart 2.—Eleven substances are listed comparing the subject and group mean of 12 weekly determinations in 1965 and listing one and two standard deviations of each substance. Each subject thus graphically tabulated was unique from the 11 others in the same group. Biologic values are given in units per 100 ml.

Each bar-graph is placed in relative position to the heavy vertical line which acts as the group mean. Not indicated is the group SD which, as expected, is wider than the individual SD.

Recently, Williams,[4] in describing the effects of laboratory automation in clinical medicine, presented in chart form a hypothetical example of an individual's biologic chemistry profile. This chart gives base-line values which can be used in comparison with subsequent changes of specific tests. In a similar manner our data on 48 individuals can be used as a base-line for future reference.

In Tables 1, 2 and 3 we find for seven blood values the M, 1 SD and CV given for three individuals in the first group each over a three-year period. The patient in Table 1 can be seen to have a wide SD and CV in 1965 for hematocrit (less for hemoglobin) because she donated a pint of blood in February. It may be pointed out that the CV presented in each individual is illustrative of physiologic or biologic variance, which of necessity must include technical variance. Other figures and charts thus prepared graphically illustrate and further emphasize the concept of individual chemical or hematologic characteristics.

In Table 4 are found nine values obtained from pooled serum in 1965 over an 11-week period representing only a part of our quality control program.

The stated physiologic variance for the first five values given in Tables 1, 2 and 3 for 1965 must be compared with similar values in Table 4 which reflect the technical variance of identical tests. For example, the glucose variance of 1.6 percent in Table 4 when subtracted from the glucose variance of 9.6 percent in Table 1 will give us a true physiological variance of 8 percent. The other four values can be similarly evaluated. The SD and CV for the first five quality control values noted in Table 4 for 1965 can be seen to be less than those for the 1965 values depicted in Tables 1, 2 and 3, except for the cholesterol values noted in Table 2.

Normal values as observed at Sutter Community Hospitals are shown in Table 5.

TABLE 3.—*Values similar to those noted in Table 1 and 2, a 46 year old male. Biologic values are expressed per 100 ml. Relatively narrow ranges of values are maintained over a three-year period.*

		1965	1966	1967
Glucose mg	M	85	80	85
	1SD	9	4.4	4.0
	CV%	10	5.5	4.7
Urea Nitrogen mg	M	17	16	17
	1SD	1.7	2.2	2.0
	CV%	10	14	11.8
Uric Acid mg	M	5.8	5.8	6.1
	1SD	0.53	0.08	0.34
	CV%	9.1	1.3	5.5
Cholesterol mg	M	198	198	205
	1SD	14.3	13.7	9.73
	CV%	7.2	6.9	4.7
Oxalacetic Transaminase (Karmen Units)	M	27	14	21
	1SD	3.5	3.3	2.43
	CV%	13	23	11.5
Hemoglobin gm	M	15.3	15.0	15.4
	1SD	0.11	0.49	0.45
	CV%	0.7	3.2	2.9
Hematocrit mm	M	48	47	47
	1SD	1.28	3.8	1.08
	CV%	2.7	8.1	2.3

TABLE 4.—*Quality control values are listed as a result of determinations performed on a pooled serum from 11 weekly determinations in January-February-March 1965, showing the mean (M), one and two standard deviations (SD) and coefficient of variation (CV). The CV as a variance can be noted to be much narrower than the physiological variations listed in other tables. A complete quality control program is a most essential part of evaluating the precision and accuracy of a laboratory. Values are expressed in the usual mg, gm and units per 100 ml.*

	M	1 SD	2 SD	CV
Glucose	61	1.0	2.0	1.6%
Urea Nitrogen	16	0.31	0.6	1.9%
Uric Acid	3.1	0.07	0.14	2.2%
Cholesterol	128	8.2	16.4	6.4%
Glutamic Oxalacetic Transaminase (Karmen Units)	18	2.0	4.0	11.2%
Alkaline Phosphatase (Babson-Reed Units)	0.9	0.24	0.5	27.0%
Albumin	2.9	0.09	0.18	3.1%
Globulin	1.3	0.09	0.18	6.9%
Total Protein	4.1	0.11	0.2	2.7%

TABLE 5.—*Normal Values as Observed in Sutter Community Hospitals*

	Range per 100 ml
Glucose	75-110 mg
Urea Nitrogen	6-23 mg
Uric Acid	3-6 mg
Cholesterol	150-250 mg
Oxalacetic Transaminase (Karmen Units)	up to 40 Karmen Units
Alkaline Phosphatase (Babson-Reed Units)	1.5-4 Babson-Reed Units
Albumin	4.5-5.5 gm
Globulin	1.5-3.0 gm
Total Protein	6-8 gm
Hemoglobin	M 14-18 gm F 12-16 gm
Hematocrit, percent	M 42-52 F 37-47

Procedures those of routine Technicon N methods. Hemoglobin by cyanmethemoglobin method.

Discussion

The values given above in figures and tables actually form only a small amount of the data that are to be obtained. Several points may be emphasized.

- Each individual has a specific and distinctive pattern of biologic values.
- It is probable that no two individuals are identical in this regard.
- Individual (intrapersonal) mean, standard deviation and coefficient of variation have narrower ranges than similar (interpersonal) group values.
- These group values are again narrower than population values.
- Much has yet to be learned about the parameters of "normal" laboratory values.

It is anticipated that the survey will continue for several more years in order to study possible variations with age, sex, ethnic background and time in specific individuals. It is also likely that some variation in the method of study will be made for subsequent comparison with previous values obtained. This variation in time over the years may present us with much information not yet available. This study would not have been possible without the use of automated equipment which has the value of performing a large number of tests in a uniform manner at a reasonable cost. The potential of such automation has not yet been reached and with the addition of computers the retrieval of information is infinitely greater.

Williams showed that many tests repeated on individuals over long periods may reveal a similar constancy compared with the wider range for a healthy population. The results of our test patterns noted above have confirmed the relative individuality of these test patterns and indicate the desirability of expanding the number of procedures and involving a larger number of people. For uniformity and comparability of results from one time to another on the same person and for comparison of individuals, continuous quality control and a careful evaluation of the performance limits of each test are necessary. This must of necessity apply to automated procedures.

It is possible that such a study might allow us to predict the development of various disorders before clinically apparent. One might expect that "pre-diabetes" might be more easily detected. One of many blood urea nitrogen determinations may be abnormal enough to warrant further evaluation of possible renal disease. Serial determinations of serum alkaline phosphatase may reveal early hepatic disease. We are all aware of the changes of the serum glutamic oxalacetic transaminase and lactic dehydrogenase as myocardial infarction develops and then progresses. Determining a newborn's blood phenylaline level will allow the detection of phenylketonuria (PKU) before clinical evidence of disease. Many such additional examples may be given. A study such as applied above must be done with the realization that inherent problems are present, several of which are:

- It is essential that blood be obtained from completely "healthy" persons ("healthy" to be defined).
- The technique must be well established and accurate with good precision.
- An adequate quality control program must be a part of such a study.
- The chemical values of many tests will vary with the method and instruments being used.
- The time that the blood (urine, spinal fluid, etc.) is withdrawn may produce variables due to diet, drugs, diurnal variations, etc.
- Some medications will interfere with certain test values.
- Further work is necessary to improve precision, accuracy and quality control in medical laboratories.

At a recent conference[3] on "Normal Laboratory Test Profiles," held at the National Institutes of Health, other laboratories and hospital groups are now cooperating in this endeavor with the expectation that more accumulated data will be obtained to be used as a guide in further defining normal values.

REFERENCES

1. Williams, G. Z.: Clinical Pathology Tomorrow, Am. J. Clin. Path., 37:121, Feb. 1962.
2. Perry, T. M., Williams, G. Z., and Kupfer, H. G.: Clinical pathology tests in health evaluation, AMA Pamphlet, 1961, p. 6.
3. Williams, G. Z.: Workshop conference on normal laboratory test profiles, National Institute of General Medicine Sciences, Bethesda, Maryland, June 1-2, 1967.
4. Williams, G. Z.: Effects of automation on laboratory diagnosis, Calif. Med., 108:43-45, Jan. 1968.

Cardiac Monitoring in a Community Hospital

Analysis of 18 Months' Experience

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■ *Cardiac monitoring facilities have been present in teaching hospital centers for over five years. A substantial decrease in mortality has been observed in monitored patients with acute myocardial infarction. The community hospital system offers a challenge to effective monitoring since many physicians care for patients and often many kinds of therapy are used.*

After 18 months of operation mortality from myocardial infarction was only 16.6 percent in a community hospital monitoring unit where the majority of the emergency care and resnscitation was carried out by nurses. Vital to this success was the nse of standing orders for nurses, requirement of privilege to practice within the monitoring facility and acceptance of the nurse as a therapist in emergency situations.

Fourteen patients were snccessfnlly resuscitated and were later discharged from the hospital. Four of them had ventricular fibrillation from digitalis intoxication.

Patients with shock and severe congestive heart failnre continue to be a major nnsolved clinical problem. The results indicate that the potentially viable patient with serious electrical distnrbances can almost invariably be salvaged.

THREE RECENT DEVELOPMENTS have been responsible for the institution of electronic monitoring facilities for patients with acute myocardial infarction. First is the availability of competent means of closed-chest massage and artificial ventilation. The second is the development and miniaturization of equipment capable of monitoring the electrocardiogram and other physiologic variables. Last is the realization that electrical rhythm disturbances constitute a major hazard to the patient with acute myocardial infarction. Many centers

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throughout this and other countries have initiated such units and have published the results of their experiences. [2,3,5-8,10,11,12,13]

Organization

In March of 1966 a monitoring facility was begun at Sutter Memorial Hospital, a 271-bed hospital without intern or resident staff. Planning and organization were directed by a committee of practicing physicians. Because of space limitations, four private rooms on a medical-surgical ward were equipped with conduits and wired for monitoring beds. Four more rooms were added later. The private room concept permitted solitude for the patient, yet rooms were within 30 feet of the nurses' station and access to resuscitation. Each room contained a cardiotachometer* with manual rate alarm setting, a line current-driven internal-external pacemaker, and a 5-inch oscilloscope mounted on wall brackets. No audible signal was present in the patient's room. A telephone jack in the wall bracket allowed a plug insert for synchronized DC shock. Inputs from the patient entered a wall faceplate, and conduit was run from this point to the monitoring equipment. Individual rooms were revamped to provide overhead lighting and eight major electrical outlets. Excess furniture was removed and suction equipment and manometers were added. An intercom system connected these rooms with the main nursing station and with the monitoring station. A completely equipped emergency cart with battery pacemaker, DC defibrillator, suction, bedboard, manual breathing bag, cardiac medications and other necessary equipment was immediately available in the hall.

A separate nursing station was constructed to contain the slave oscilloscopes, patient alarm and direct-writing recorder. It was stocked with medication necessary for patient care. One trained registered nurse was assigned for every two patients within the monitoring facility. Convalescent patients with cardiac disease and other patients confined to the ward were cared for by nurses working at the main station.

Patients were admitted to the monitoring facility at the request of their referring physician. Any patient with an acute myocardial infarction, regardless of clinical condition, was accepted. Those patients in whom infarctions were not proven were transferred as soon as possible. Patients without infarctions but with heart disease and rhythm disturbances deemed harmful were also accepted. After discharge from the unit, patients convalescing from infarctions or from major arrhythmias were kept on the same ward as long as possible in order to take advantage of the equipment and nursing experience should serious rhythm disturbances develop later.

Nurses working within the unit were initially given a 30-hour didactic lecture series. In addition, they were instructed in the principles of intravenous therapy and in the taking of standard electrocardiograms. As part of their training, they performed elective cardioversions in the operating room under the supervision of a physician. In anticipation of the responsibility delegated to these nurses, a pay scale for them similar to that of surgical nurses was agreed upon by the hospital administration.

Physicians wishing to admit and to care for patients within the monitoring facility were granted privileges to do so only after instruction in cardiopulmonary resuscitation and in the use of the electrical equipment. In order to assure physician coverage and attendance at any cardiac arrest, a double-call system was arranged. In the event of a resuscitation emergency both the attending physician and the unit director or his appointee were called.

Each patient's electrocardiogram was continuously monitored by precordial electrodes held firmly with paper tape. The monitor was routinely set to alarm at rates above 150 or below 40 with a 7-second preset delay. A photoelectric cell was placed on the ear lobe for qualitative assessment of arterial pressure. This was necessary since occasionally adequate electrocardiograms could not be obtained and deterioration of cardiac function might be evidenced by decline in arterial pressure before electrical deterioration. Whenever possible a nurse was present within the monitoring unit station to view the electrocardiographic traces on the oscilloscope. In this way any trend toward potentially dangerous rhythm disturbances could be noted and the physician notified. On occasion, cardiac arrest was predicted from this viewing of the tracing, and the nurses arrived in the patient's room before the alarm sounded.

The duties and responsibilities of the monitoring unit nurses during cardiac arrest were set forth in written rules of procedure (Table 1). Nurses im-

*Sanborn Division, Hewlett-Packard Co.

TABLE 1.—*Procedure to Follow during Cardiac Arrest in Monitoring Unit*

1. Establish BP, level of consciousness, pulse, nature of rhythm on oscilloscope.
2. *(a) Ventricular tachycardia*
 Massage and ventilate; Lidocaine 100 mg. IV; HCO_3 45 mEq IV; BP support with Metaraminol 100 mg./liter; if shock or unconsciousness, synchronized countershock.
 (b) Ventricular fibrillation
 Immediate DC countershock followed by massage and ventilation; HCO_3 45 mEq IV; Lidocaine and Metaraminol if needed.
 (c) Cardiac asystole or complete heart block with slow ventricular rate
 Massage and ventilation; external pacing if no response; HCO_3 45 mEq IV and isoproterenol 1 ampule (0.2 mg.) or epinephrine 0.5 mg. IV for asystole; isoproterenol 1 mg./liter titrated at 1 cc/min initially for heart block.
 (d) Rapid atrial fibrillation; atrial tachycardia
 Massage and ventilation; HCO_3 45 mEq IV; synchronized shock if condition critical and physician not available.
 (e) PVCs, bursts of ventricular tachycardia
 50-200 mg. bolus IV Lidocaine
3. Nurses are allowed under urgent circumstances to institute pacing or electrical shock, administer medication or to follow prior written directions from the attending physician.

MONITORING UNIT COMMITTEE

mediately begin ventilatory and circulatory support with mouth-to-mouth or bag breathing and closed-chest massage. In cardiac asystole they are authorized to administer intravenously 0.2 mg of isoproterenol or 0.5 mg of epinephrine. The same drugs are titrated intravenously if complete heart block is present. If there is no response, external pacing may be begun. Our experience has led us to believe that no time should be wasted in administering shock to a patient with ventricular fibrillation. Timed drills showed that equipment could be moved into the patient's room, assembled and activated in 45 seconds. Therefore nurses first attempt to defibrillate the patient and then begin resuscitation. Intravenous solutions are running slowly in all patients within the monitoring facility and the nurses are authorized to give intravenous sodium bicarbonate during resuscitative therapy. Lidocaine drips may be manipulated so as to suppress abnormal rhythms. All these measures take place in the absence of a physician, and upon his arrival further therapy is at his discretion.

Results

Information on 241 patients with myocardial infarction monitored for an average of five days is included in Table 2. Fifty had cardiac arrest which, regardless of mechanism, is defined as failure of the circulation — invariably fatal unless adequate resuscitative measures are effected. Twenty-three patients were successfully resuscitated, surviving over 24 hours. Ten of these were discharged ambulatory. Mortality in the hospital for the 241 patients was 16.6 percent whereas for unmonitored patients with myocardial infarction during the same period (Table 3) the mortality was 26.2 percent, with no survivors from cardiac arrest. Review of 240 patients with myocardial infarction seen at this hospital from February 1963 to February 1966 showed an overall hospital mortality of 24.2 percent. This group is mentioned for comparison alone since only limited conclusions can be drawn from these figures and the group does not constitute a valid control.

TABLE 2.—*Cardiac Monitoring Unit (March 1966-August 1967)*

517 patients admitted
50 arrests
23 successful resuscitations
10 survivors
mortality 16.6%

Arrest	*Time*	*Survivors*
9	4 hrs	2
4	12 hrs	–
9	24 hrs	2
4	48 hrs	2
8	72 hrs	3
6	1 week	1
10	over 2 week	–

*Arrhythmias recognized (87.4% of patients)**

	No.
1° block	16
2° block	8
complete heart block	18
atrial prematures	90
nodal rhythm	16
sinus bradycardia	8
atrial tachycardia	13
atrial flutter	25
atrial fibrillation	68
PVCs	174
ventricular tachycardia	32
ventricular fibrillation	23
ventricular standstill	12

*Many patients exhibited multiple arrhythmias.

TABLE 3.—*Unmonitored Patients with Myocardial Infarction (March 1966-August 1967)*

62 patients
16 deaths
mortality 26.2%

Time of death	*No. of patients*	*Arrhythmias defined*	*No. of patients*
1st day	5	atrial fibrillation	3
2nd day	4	atrial tachycardia	1
5th day	2	PVCs	2
1st week	2	ventricular tachycardia	1
		ventricular fibrillation	1

However, a progressive decrease in mortality was noted during each half-year period (Table 4). There was little change in the first six months of operation but a striking improvement was apparent after 18 months. Several factors may have contributed to this increased survival. First, changes in mortality were first apparent after the initial six months of unit operation, the time at which routine standing orders were instituted for emergencies. Second, there was decrease in the number of cardiac arrests. Although successful resuscitation was more frequent, the proportion of survivors did not change appreciably. Therefore prevention may have played as important a role as resuscitation.

Clinical status

Clinical summaries of resuscitated patients are presented in Table 5. The monitored patients who survived seemed to follow a pattern of mild to moderate disease with sudden and catastrophic interference with electrical function and automaticity. All had rhythm disturbances but few appeared to have severe depression of myocardial function. None of them had congestive failure or sustained shock before the onset of rhythm disturbance. In the majority of the surviving patients cardiac arrest had occurred within the first 72 hours of admission. Patients in whom arrest did not occur until a week or more after admission almost invariably died.

Severe shock or congestive heart failure was present in all but five patients who died. The mortality of patients with shock and failure was unimproved when compared with mortality before the monitoring unit was opened. In these patients a variety of primarily ventricular rhythm disturbances was observed before death. Although in a number of cases these disturbances were temporarily reverted by appropriate therapy, survival was not effected. These rhythms therefore were felt to be agonal and indicative of ventricular failure and death.

Avoidable deaths

In four instances, all within the first year of operation, it appeared on review that death might have been prevented. In one patient who died while in the monitoring facility there was inadequate appreciation of the importance of progressive bradycardia, and refractive ventricular standstill occurred. Of the 40 patients who died, nine did so after discharge from the monitoring facility. In three of these cases, summarized below, death appeared preventable.

CASE A.—A 67-year-old woman entered the hospital hypotensive and with electrocardiographic evidence of acute anteroseptal infarct. Congestive failure and atrial fibrillation developed. Digitalis was begun but high grade AV block developed and the drug was discontinued. Because of steady clinical deterioration, a transvenous pacemaker was inserted on the fourth hospital day. After two days with the pacemaker, sinus rhythm was restored. Her condition improved and she was discharged from the monitoring unit after 16 days. Two days later, while sitting in a chair, she suddenly became cyanotic and unconscious. An electrocardiogram showed ventricular fibrillation and resuscitation was unsuccessful.

CASE B.—A 62-year-old man with previous myocardial infarction seven years before, began having increasing chest pain and shortness of breath. An electrocardiogram showed inferior and anterior wall injury. Digitalis was administered. After five days, he was discharged from the unit. Three days later, while he was using the bed pan, cardiac arrest occurred. No electrical activity was evident on electrocardiogram and resuscitation was unsuccessful.

TABLE 4.—*Data on Survival of Patients in Cardiac Monitoring Unit*

Date	*Infarctions*	*Arrests*	*Successful Resuscitation*	*Survivors*	*Deaths*	*Percent*
3-8/66	74	21	5	2	16	21.6
9/66-2/67	81	16	8	3	14	15.9
3-8/67	79	13	10	5	10	12.7

Case C.—A 60-year-old man with hypertension had onset of crushing anterior chest pain four hours before admission, with electrocardiographic evidence of acute inferior wall infarction. Digitalis was started when atrial tachycardia began. Three days later, there was evidence of a high degree AV block with a ventricular rate of 70. Digitalis was discontinued. Monitoring continued for ten days and the patient was discharged from the unit in sinus rhythm. Following discharge a gallop developed, and then left ventricular failure. Digitalis was again started. On the 16th day in hospital, there was sudden electrical arrest and death.

Superventricular rhythm disturbances

The importance of ventricular rhythm disturbances and of complete heart block has been well established. However, in patients with acute myocardial infarction, ventricular arrhythmia is not the only lethal arrhythmia. Three important atrial rhythm disturbances were noted in this series: Sino-atrial failure, refractive atrial tachycardia, and sinus or nodal bradycardia leading to ventricular standstill or to ventricular escape with ventricular tachycardia.

Sinus node failure is defined electrically as intermittent or permanent loss of sinus discharge with or without nodal capture. The subsequent pacemaker discharge is usually slow and cardiac output inadequate. This arrhythmia occurred in three patients. An unusual example is shown in Figure 1. Conversion of atrial tachycardia resulted in sinus bradycardia and sinus arrest. Hypotension developed and circulatory adequacy was restored only following return to atrial tachycardia. Postmortem examination showed anterior, inferior and atrial infarctions.

Refractory atrial tachycardia led to death in

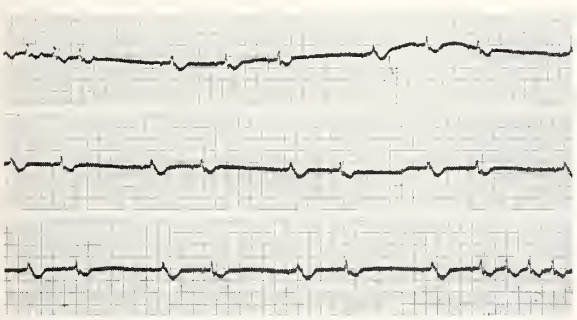


Figure 1.—Sino-atrial failure. Atrial tachcardia is interrupted by sinus arrest and sinus bradycardia. Hypotension ensued and circulatory adequacy returned only during atrial tachycardia.

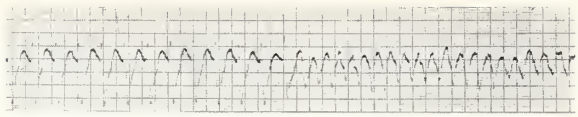


Figure 2.—Sudden transformation of atrial tachycardia with aberrant ventricular response to ventricular fibrillation.

three patients. Although a common disturbance of rhythm, this is an uncommonly severe complication of myocardial infarction. Previous studies have attested the circulatory inadequacy produced by the rapid ventricular rate.[12] For the diseased heart, this represents an exaggerated oxygen need. As shown in Figure 2, the rhythm disturbance may abruptly lead to serious ventricular rhythm abnormalities and death. In these three patients massive intravenous doses of procaine amide, quinidine and lidocaine and frequent electric countershock were unsuccessful.

In patients with myocardial necrosis, a critical ventricular rate may be necessary to suppress ventricular escape and ectopy.[9] Reduction in rate may allow reentry beats to drive the heart (Figure 3). Contrarily, slow rates of sinus or nodal origin may terminate in electrical arrest. Such rate-dependent phenomena were found in three patients, one of whom progressed to cardiac arrest and in one of whom unresponsive ventricular tachycardia developed. Knowledge or prediction of such slowing may have prompted appropriate therapy and salvage.

Patients without infarction

Monitoring was requested for a number of patients without myocardial infarction. Summaries

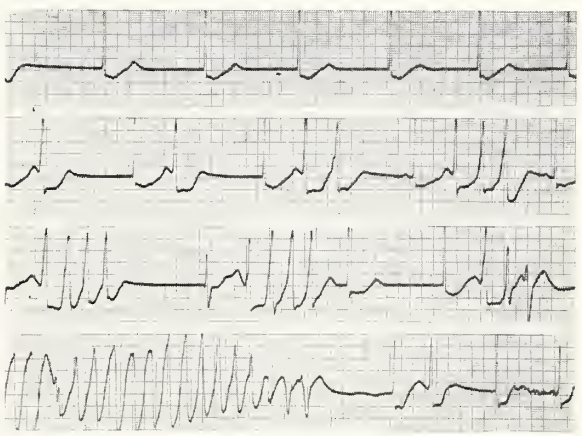


Figure 3.—Nodal bradycardia with ventricular premature beats, bursts of ventricular tachycardia and sudden onset of ventricular fibrillation with spontaneous reversion.

TABLE 5.—*Clinical Data on Resuscitated Patients in Cardiac Monitoring Unit*

				Patients with Myocardial Infarction				
Case	*Age and Sex*	*Pathology*	*Rhythm*	*Shock*	*CHF*	*Therapy*	*Time of Monitor*	*Comments*
1	72 M	Posterior MI	Atrial tachycardia; sinus arrest and bradycardia	Yes	Yes	Shock, lidocaine, HCO_3	5 days	Died; bilateral coronary occlusions; anterior, inferior and atrial infarcts.
2	56 M	Anterolateral MI	Ventricular tachycardia	. . .	. . .	Massage, HCO_3, quinidine, lidocaine	8 days	Survived.
3	58 F	Posterior MI	Ventricular fibrillation CHB, PVCs	. . .	. . .	Shock, lidocaine, HCO_3, procaine amide, quinidine	10 days	Survived; ventricular fibrillation and infarction following selective injection RCA.
4	68 M	Inferior MI	Intractable atrial tachycardia	. . .	Yes	Shock, lidocaine, quinidine, digitalis, procaine amide, diphenylhydantoin	11 days	Died 4 days after discharge from unit.
5	74 F	Inferior MI	Ventricular fibrillation	Yes	. . .	Shock, lidocaine, HCO_3	8 days	Died in renal failure; terminal ventricular fibrillation.
6	67 F	Anterior MI	Atrial fibrillation, CHB; ventricular fibrillation	Yes	Yes	Pacemaker, catheter	16 days	Died in ventricular fibrillation 2 days after discharge from unit; bilateral coronary thrombi.
7	59 M	Anterolateral MI	PVCs, CHB, ventricular fibrillation	Yes	Yes	Shock, lidocaine, HCO_3 digitalis	3 days	Died; 3 prior infarcts; bilateral coronary occlusions.
8	78 M	Anterior MI	Ventricular fibrillation, CHB	Yes	. . .	Shock, lidocaine	5 days	Died.
9	64 M	LBBB; infarct by enzymes and history	Ventricular tachycardia, fibrillation	. .	Yes	Shock, lidocaine	11 days	Died.
10	66 M	Anterior MI	Atrial tachycardia	Yes	. . .	Shock, metaraminol, quinidine	6 days	Survived; died 9 months later.
11	79 M	Inferior MI	CHB	Yes	Yes	Pacemaker, catheter, digitalis	8 days	Died; refractive failure and unresponsiveness to pacing.
12	42 M	Inferior MI	Ventricular fibrillation	. .	Yes	Shock, lidocaine, digitalis	10 days	Died; ventricular fibrillation 6 hours after transfer from unit; intractable failure.
13	62 M	Anterolateral MI	Ventricular standstill	. . .	. . .	Isoproterenol	8 days	Survived; subsequent Vineberg procedure.
14	78 F	Inferolateral MI	Ventricular fibrillation	Yes	. . .	Shock, lidocaine, HCO_3	5 days	Survived.
15	58 M	Inferior MI	CHB	Yes	. . .	Isoproterenol	6 days	Survived, working.
16	49 M	Anterior MI	Atrial tachycardia; ventricular standstill	Yes	Yes	Shock, procaine amide, isoproterenol	2 days	Died; diabetic; 2 prior infarcts.
17	63 F	Anterolateral MI	Ventricular fibrillation	. . .	. . .	Shock, lidocaine, HCO_3	6 days	Survived; working.

18	63 M	Anterior MI	PVCs, ventricular tachycardia	. . .	. . .	Procaine amide, shock	5 days	Died 72 hours after discharge from unit; ventricular fibrillation.
19	55 M	Anterior MI	Progressive bradycardia; ventricular standstill	. . .	Yes	Pacemaker, catheter	10 days	Survived; renal shut down after arrest; now working.
20	81 M	Inferior MI	Ventricular tachycardia	. .	Yes	Closed chest massage, HCO_3	7 days	Died 5 days after discharge from unit; intractable CHF; bilateral coronary thrombi.
21	59 F	Inferior MI	Progressive bradycardia; ventricular tachycardia	Yes	. . .	Pacemaker, isoproterenol, lidocaine	3 days	Died.
22	43 M	Anterior MI	Ventricular tachycardia, CHB	. . .	. . .	Shock, pacemaker, catheter	7 days	Survived.
23	54 F	Anterior subendocardial MI	Ventricular tachycardia; ventricular fibrillation	. . .	. . .	Shock, HCO_3, lidocaine	7 days	Survived; diabetic.
				Patients without Infarction				
24	77 M	ASHD without infarct	CHB; ventricular fibrillation	Yes	Yes	Pacemaker, catheter, shock quinidine	3 days	Died.
25	44 M	RHD, mitral valve replacement	Ventricular tachycardia	Yes	Yes	Shock, digitalis, quinidine, ethacrynic acid, lidocaine	3 days	Died in intractable CHF.
26	75 F	. . .	Paroxysmal ventricular fibrillation; sinus bradycardia	. . .	. . .	Shock, lidocaine, ephedrine, digitalis	8 days	Survived; ? digitalis intoxication.
27	43 F	RHD post mitral commissurotomy	Ventricular tachycardia and fibrillation; sinoatrial failure	. . .	. . .	Shock	4 days	Survived; digitalis intoxication; now working.
28	53 F	RHD, mitral valve replacement	Ventricular tachycardia and fibrillation; CHB	Yes	. .	Shock, quinidine, lidocaine, HCO_3, diphenylhydantoin, pacemaker, catheter	7 days	Survived; digitalis intoxication manifest 3 days after conversion from atrial fibrillation; now working.
29	63 M	ASHD	Ventricular bigeminy and fibrillation	. .	Yes	Shock, lidocaine, atropine	8 days	Survived; digitalis intoxication.
30	64 F	Aortic stenosis	Ventricular fibrillation	. . .	. . .	Shock, lidocaine, pacemaker, quinidine	2 days	Died; intractable ventricular fibrillation with over 40 individual conversions.

LEGEND

ASHD	arteriosclerotic heart disease
CHB	complete heart block
CHF	congestive heart failure
HCO_3	bicarbonate
LBBB	left bundle branch block
MI	myocardial infarction
PVC	premature ventricular contraction
RCA	right coronary artery
RHD	rheumatic heart disease

of their cases are included in Table 5. These included patients with rheumatic heart disease with atrial fibrillation, patients with digitalis or quinidine intoxication, with paroxysmal rhythm disturbances or complete heart block, and patients with severe aortic stenosis exhibiting Stokes-Adams disease. Cardiac arrest occurred in seven of this group, with successful resuscitation in four. In all four survivors, the supposed mechanism of arrest was ventricular tachycardia or fibrillation due to digitalis intoxication.

Discussion

The results in this group of patients seem to justify the monitoring unit concept, since prevention and therapy of lethal cardiac arrhythmias were large factors in the decrease in mortality. This reduction parallels that found in other series and indicates that a successful program can exist in a community hospital without intern or resident staff where emergency resuscitation is carried out primarily by nurses. Obviously such results represent an understanding and an adaptation to the needs and problems of the community hospital system. The design and organization of such a unit must differ from facilities present in teaching hospitals where full time staff and training physicians are constantly present.

First of all there must be a uniform policy for arrest and resuscitation therapy. When many physicians treat patients, as many manners of care may be found. Analysis of the statistics for the initial six months pointed to a failure of resuscitation in the majority of patients. This failure was attributed to lack of a uniform approach to treatment. After we established a routine policy in cardiac arrest based upon the patient's clinical condition and the arrhythmia present, mortality was substantially improved. Routine orders for cases of arrest enabled nurses to proceed promptly and intelligently during emergencies. This ability is vitally important, since emergency calls may be answered by physicians who ordinarily do not deal with patients with heart disease and who therefore may not be helpful.

Second, to insure a high level of patient care, privileges must be granted to care for patients within the unit. Persons certified to give such care have displayed skill in therapy of patients and familiarity with rhythm disturbances, cardiac drugs, electrical monitoring and therapeutic equipment.

Third, nursing training must not focus only on basic science and interpretation of the electrocardiogram. Rather the emphasis needs to be placed on anticipation and recognition of clinical deterioration, active resuscitation and the use of pacemakers and defibrillators. The training of nurses should not be intended to make them assistants but active participants and therapists in an emergency when a physician is not available. At this point, it may be appropriate to mention that within the last year 13 of 18 successful resuscitations were performed entirely by nursing staff before the arrival of a physician.

The decrease in mortality noted in this and other series quickens interest in how the death rate might be further reduced. If our ten survivors were added to mortality statistics from myocardial infarction, the overall risk of 20.8 percent would not differ greatly from previous results. Monitoring units therefore seem to assure the salvage of viable patients. In patients with shock and congestive heart failure, no appreciable change has been noted since the monitoring unit was organized, and the need for more adequate pharmacologic tools or for assisted circulatory devices is clear.

However, this study indicates several potential ways in which the death rate may be reduced in other potentially viable patients. First, early hospital admission of persons with suspected myocardial infarction is essential. The frequency of lethal ventricular arrhythmia soon after infarction has been stressed.[8] Serious arrhythmia often has been demonstrated either at home or in the hospital within the first few hours after admission.[1,14] In our experience, arrest occurred within the first 24 hours in 23 cases, and four of the patients were revived. Physicians suspecting myocardial infarction may well reduce mortality by prompt action.

Second, patients with infarction appear to fall into three general categories — called here, Groups 1, 2 and 3 — and the category dictates to a great extent the aggressiveness of therapy, the length of monitoring and the possibility of survival. Guided by the clinical appearance of the patient, the nursing staff can predict his course and plot the appropriate therapy necessary.

Group 1 patients are those with sudden catastrophic rhythm disturbances occurring usually within 72 hours after admission. Ventricular function is assumed to be adequate since resuscitation is usually not difficult. None of these patients in the series here reported had persistent shock or

failure and only one of nine died. Patients with rhythm disturbance of this type are few in number.

Group 2 patients have frequent unpredictable changes in rhythm for periods as long as two weeks after infarction. In our series shock and failure were present in patients of this order and were only tenuously controlled by medication. For these patients prolonged monitoring was required. Since the risk of recurrence of arrhythmias was high after discharge, telemetric monitoring for the duration of stay in hospital has been suggested. Arrest in these patients was poorly tolerated and more difficult to reverse and only two have survived.

Group 3 patients have irreversible myocardial damage, shock and congestive heart failure. Rhythm disturbances may be altered but survival is not effected. Therefore emphasis is placed on distinguishing Type 1 and Type 2 patients. The former are discharged from monitoring in four to five days if no significant rhythm disturbances are noted. Patients in Group 2 are monitored for more than one week.

Third, potentially viable patients may be lost in the post-monitoring period. Almost 20 percent of our subjects who died did so after discharge from the unit. As was previously mentioned, three deaths appeared preventable. Consequently it has been our policy to leave convalescent patients with impaired myocardial function or previous arrhythmia on the ward as long as possible to take advantage of equipment and personnel available. All RNs working on the convalescent ward have monitoring unit training and experience. A telemetric system compatible with our monitoring equipment has been purchased.

Finally, our results have suggested that a greater emphasis must be placed on rhythm disturbances previously considered benign. Sino-atrial arrest, atrial tachycardia and sinus and nodal bradycardia may less abruptly and dramatically produce cardiac deterioration, and perhaps it is the fact that they are initially tolerated well which leads to complacency and to a lessened sense of therapeutic urgency. However, suitable treatment should be instituted as quickly as possible, with the same aggressive approach as for ventricular arrhythmias.

There appears to be no reason why monitoring should be restricted only to those with myocardial necrosis. Admission should be governed primarily by need and by the availability of bed space. Our experience with resuscitation of patients with digitalis-induced ventricular tachycardia and fibrillation is impressive since these arrhythmias have not previously responded to electric countershock and are frequently fatal.[11]

It is evident that monitoring units have made an important contribution to immediate survival of patients with rhythm disturbances of many varieties and from many causes. Yet little information is available as to the life expectancy of resuscitated patients and their ability to return to normal life.[4] Our numbers are small and the follow-up is short. However it is significant that of the 14 patients resuscitated, five have returned to work. In follow-ups ranging from one to seventeen months there has been only one death. The patient died of cardiac arrest at home.

REFERENCES

1. Bainton, C. R., and Peterson, D. R.: Deaths from coronary heart disease in persons 50 years of age and younger, New Eng. J. Med., 268:569, 14 Mar. 1963.

2. Day, H. W.: An intensive coronary care area, Dis. Chest, 44:423, Oct. 1963.

3. Day, H. W.: Effectiveness of an intensive coronary care area, Amer. J. Cardiol., 15:51, Jan. 1965.

4. Geddes, J. S., Adgey, A. A. J., and Pantridge, J. E.: Prognosis after recovery from ventricular fibrillation complicating ischemic heart disease, Lancet, 2:273, 5 Aug. 1967.

5. Goble, A. J., Sloman, G., and Robinson, G. S.: Mortality reduction in a coronary care unit, Brit. Med. J., 1:1005, 23 Apr. 1966.

6. Julian, D. C., Valentine, P. A., and Miller, G. G.: Routine ECG monitoring in acute myocardial infarction, Med. J. Aust., 1:433, 21 Mar. 1964.

7. Lanhorne, W. H.: The coronary care unit: A year's experience in a community hospital, JAMA, 201:662, 28 Aug. 1967.

8. Lawrie, D. M., Greenwood, T. W., Goddard, M., Harvey, A. C., Donald, K. W., Julian, D. G., and Oliver, M. F.: A coronary care unit in the routine management of myocardial infarction, Lancet, 2:109, 15 July 1967.

9. Linenthal, A. J., and Zoll, P. M.: Prevention of ventricular tachycardia and fibrillation by intravenous isoproterenol and epinephrine, Circulation, 27:5, Jan. 1963.

10. Lown, B., Fakro, A. M., Hood, W. B., and Thorn, G. W.: The coronary care unit: New perspectives and directions, JAMA, 199:188, 16 Jan. 1967.

11. Lown, B.: Electrical reversion of cardiac arrhythmias, Brit. Heart J., 29:469, July 1967.

12. McIntosh, H. D., Kong, Y., and Morris, J. J.: Hemodynamic effects of supraventricular arrhythmias, Amer. J. Med., 37:712, Nov. 1964.

13. Nachlas, M. M., Miller, D. I., and Siedbond, M. P.: Continuous monitoring of patients with acute myocardial infarction: A 32 month experience, JAMA, 198:1, 3 Oct. 1966.

14. Pantridge, J. F., and Geddes, J. S.: A mobile intensive-care unit in the management of myocardial infarction, Lancet, 2:271, 5 Aug. 1967.

Neonatal Cardiac Distress

A Practical Approach to Recognition, Diagnosis, and Management

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■ *The death rate among neonates with cardiovascular disease is 50 percent during the first six months, with the majority dying during the first month. With early diagnosis most of these babies could be saved. In approaching the diagnosis of cardiac distress in the newborn, it is important to remember that the types of cardiovascular disease which cause symptoms and death early in life are quite different from those in older children. Lesions such as hypoplasia of the left heart, transposition of the great arteries, endocardial fibroelastosis, pulmonary atresia, mitral atresia, tricuspid atresia and truncus arteriosus are common, not rare, causes of cardiac distress in the newborn.*

A classification of neonatal cardiovascular diseases into seven pathophysiological groups is presented as a basis for an effective, practical approach to the differential diagnosis of the potentially lethal lesions. This approach is simplified further since over 90 percent of babies with cardiac distress have one of three lesions: (1) Large left-to-right shunt (characterized by the presence of massive plethora on the chest roentgenogram), (2) Large right-to-left shunt (association with intense cyanosis) or (3) Severe obstruction (including hypoplasia of the left heart, which is the most common cause of death due to cardiac distress during the first week of life).

THE EARLY RECOGNITION of cardiovascular disease in neonates is difficult but extremely important since the natural attrition rate is 50 percent during the first six months, with most deaths occurring during the first month.[31] If there is early recognition of the problem, most of these babies can be salvaged by aggressive diagnostic and surgical management.[13]

When should a serious cardiovascular lesion be suspected, how is the differential diagnosis made and what can be done for potentially lethal cardiac disease in the neonate? The basis of a practical approach to these questions is the classification of neonatal heart disease into seven lethal lesions as listed in Table 1. This classification stresses the physiological, not the anatomical, abnormality and is more helpful to the clinician since the physiology of these lesions is more pertinent to the clinical findings and course.[15]

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TABLE 1.—*Neonatal Cardiac Distress—The Seven Lethal Lesions*

Lesion	*Diagnostic Tip Off*	*Differential Diagnosis* — *Acyanotic*	*Differential Diagnosis* — *Cyanotic*	*Treatment*
1. LEFT-TO-RIGHT SHUNT	X-ray (plethora)	ASD, VSD, PDA, AV Communis, AP Window, AV Fistula	SV, Truncus, Incomplete Trans., *TA* (type C), *TAPVD**	Division or repair Band Septoplasty Transplantation
2. RIGHT-TO-LEFT SHUNT	Cyanosis		Trans., TOF, *TA, PS,* PA, *Ebstein's*	Septectomy Shunt Valvuloplasty Glenn
3. OBSTRUCTION	Electrocardiogram (hypertrophy)			
a. Without systemic hypoperfusion		Coarc., AS, MS, *PS*	*HLH* (Ao Atresia), MA, *TAPVD* below diaphragm, *TA*	Aortoplasty Valvuloplasty Septectomy
b. With systemic hypoperfusion	Pulses (weak or absent)	Hypoplastic Ao without ductus	*HLH* without ductus	?Shunt + Band
4. PRIMARY MYOCARDIAL DISEASE	X-ray (cardiac enlargement) No murmur Epigastric impulse	EFE, Myocarditis, Ab. Lt. Cor., Glycogen Storage, Cor. vas., Idio. Hyper., Vent. Diverticulum, (Pericardial Dis.)		Digitalis Ligation Excision
5. REGURGITATION	Murmur	MI, AI, PI		?Valvuloplasty ?Replacement
6. AIRWAY OBSTRUCTION	Stridor	Vascular ring		Division
7. ARRHYTHMIAS	Electrocardiogram	PAT (WPW), Flutter, Block (Corr. trans.)	*(Ebstein's)*	Digitalis Cardioversion Pacemaker

*The lesions in italic appear under more than one category.

LEGEND

Ab. Lt. Cor.=Aberrant left coronary artery; AI=Aortic insufficiency; Ao=Aorta; AP Window=Aortopulmonary window; AS=Aortic stenosis; ASD=Atrial septal defect; AV Communis=Atrioventricularis communis; AV Fistula=Arteriovenous fistula; Coarc.=Coarctation of the aorta; Corr. Trans.=Corrected transposition; Cor. Vas.=Coronary vasculitis; EFE=Endocardial fibroelastosis; Idio. Hyper.=Idiopathic hypertrophy; MI=Mitral insufficiency; MS=Mitral stenosis; PAT=Paroxysmal atrial tachycardia; PDA=Patent ductus arteriosus; PI=Pulmonary insufficiency; PS=Pulmonary stenosis; SV=Single ventricle; TA=Tricuspid atresia; TAPVD=Total anomalous pulmonary venous drainage; TOF=Tetralogy of Fallot; Trans.=Transposition of the great arteries; Vent.=Ventricular; VSD=Ventricular septal defect; WPW=Wolff-Parkinson-White syndrome.

When Should a Lesion be Suspected?

Suspicion of a cardiovascular lesion in the newborn is difficult since the signs and symptoms are usually occult.[10] Additionally, contrary to common belief, the majority of neonates with serious lesions do not have murmurs and the detection of a cardiac problem therefore depends more on inspection and palpation than on auscultation.[11] Whenever heart disease is suspected, a chest roentgenogram and an electrocardiogram should be performed and these may provide the only definite clue to the presence of a serious problem. When the physician suspects a significant cardiac lesion, pediatric cardiology consultation is indicated. In view of the limitations of physical diagnosis and because the prognosis depends on exact diagnosis, immediate or early cardiac catheterization and angiography are often advisable.[4] The important clinical, roentgenographic and electrocardiographic findings are summarized below.

Clinical Findings

Detection of pronounced cyanosis is simple and obvious; however, evaluation of minimal cyanosis can be misleading in the normally polycythemic neonate. Episodic cyanosis is almost always due to pulmonary or central nervous system disease rather than cardiac disease. The cyanotic baby who "pinks up" when placed in high tension oxygen usually has pulmonary disease but this change can also occur in cardiac babies who have interference with gaseous exchange due to congestion from left-sided decompensation. Babies with minimal right-to-left shunts have a "rosy" appearance which the unwary physician may interpret as a sign of robust good health.

Differentiation of cardiac cyanosis from cyanosis due to central nervous system disease or pulmonary disease is often dependent on the presence of other signs and symptoms of heart disease. Differential cyanosis is pathognomonic of preductal coarctation with or without transposition.[19] Chest deformity due to cardiac enlargement is rare in the neonate and is usually due to aortic atresia or a cardiac tumor. Tachypnea (resting respiratory rate greater than 40) is the earliest sign of left-sided decompensation and is usually accompanied by intercostal and sternal retractions.

Pulmonary edema should be suspected in all neonates with respiratory distress, and each should be examined carefully for other signs of cardiac disease. Airway obstruction due to a vascular ring must be suspected in babies with stridor, particularly when the stridor is intensified during nursing.

Evaluation by palpation of the peripheral pulse volume and the precordial cardiac impulse is very important but is often neglected in the newborn. The classic weak or absent femoral pulses of coarctation are well known but seldom sought. A sudden generalized decrease in pulse volume is characteristic of vasoconstriction of the ductus in a baby with hypoplasia of the left heart (HLH). Significant hemodynamic overloading is best assessed clinically by palpation of the precordial impulse. Normally, the neonatal precordial impulse is quiet and tapping and located at the xyphoid angle. In the neonate, location of the maximal cardiac impulse at the apex is pathognomonic of a left ventricular overload. A hyperdynamic impulse at the apex or xyphoid angle indicates a diastolic or volume overload (left-to-right shunt). Precordial thrills are common with ventricular septal defect, pulmonary stenosis and aortic stenosis.

Hepatomegaly is the most common sign of right-sided failure. The congested liver edge is blunt, tender and points anteriorly. A presystolic hepatic pulsation ("a" wave) is found when there is obstruction to right atrial egress as with tricuspid atresia or severe pulmonary stenosis.

Dependent edema is a rare and late sign of right-sided failure in the neonate.

As previously stated, heart murmurs are infrequent in neonates with cardiac distress, and also, contrary to common belief, the intensity of murmurs does not correlate well with the severity of disease. Although often difficult to detect, gallop rhythm is almost always present in neonates in early congestive failure.

Chest roentgenography

Roentgen examination of the neonate should usually be limited to a portable anterior posterior examination since these babies are usually in acute distress and cannot safely be moved. Lateral, oblique and barium views are seldom helpful anyway. Of paramount importance is an appreciation of the decided limitations of chest roentgenographic examination in the newborn.

The clinical findings (including the electrocardiogram) must be considered for optimal roentgen interpretation (Figure 1 and Table 2). Interpretation should include evaluation of: (1) Heart size and position, (2) Pulmonary vascular mark-

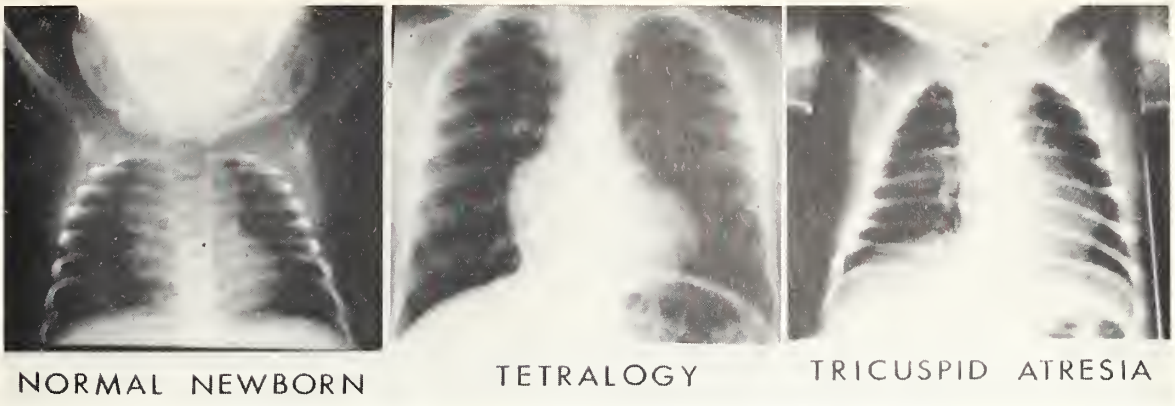


Figure 1.—Chest roentgenograms of a normal newborn, and newborns with tetralogy of Fallot and tricuspid atresia. Roentgenographic differential diagnosis without knowledge of the clinical and electrocardiographic findings is usually of limited value in the neonate.

ings, (3) Configuration of the main pulmonary artery and (4) Size and position of the aortic arch.

Cardiac enlargement should be suspected whenever the cardiothoracic ratio exceeds 60 percent; however, accurate assessment is complicated by the presence of the thymic shadow (Figure 2) and variations in heart size associated with respirations (Figure 3). In the frontal projection, right ventricular enlargement usually is associated with elevation of the cardiac apex *(cor en sabot)* and left ventricular enlargement with downward pointing of the cardiac apex. Usually the newborn with cardiac distress has generalized cardiac dilatation, and attempts to evaluate specific chamber enlargement are fruitless.

Dextrocardia and isolated levocardia are important clues to the probable presence of severe cardiac anomalies (Figure 4). Although errors are frequent, the pulmonary vascularity is classified into one of three groups — increased, normal or decreased. Both active and passive congestion can be mimicked or masked by pulmonary inflammatory disease or the respiratory distress syndrome.

Accurate roentgen or fluoroscopic differentiation of active from passive pulmonary congestion is not possible in the neonate and Kerley's B lines are rarely seen. The shadow of the main pulmonary artery is usually of increased convexity in patients with large left-to-right shunts, valvar pulmonary stenosis, pulmonary hypertension and incomplete transposition of the great vessels of the Taussig-Bing[25] or OBGVRV* types and is concaved in tetralogy and complete transposition.

The size, shape and position of the aortic arch are important in the diagnosis of certain lesions including isolated pulmonary stenosis (the aortic arch is almost always on the left), tetralogy of Fallot (the aortic arch is on the right in 34 percent of cases), coarctation of the aorta, aortic stenosis and vascular ring.

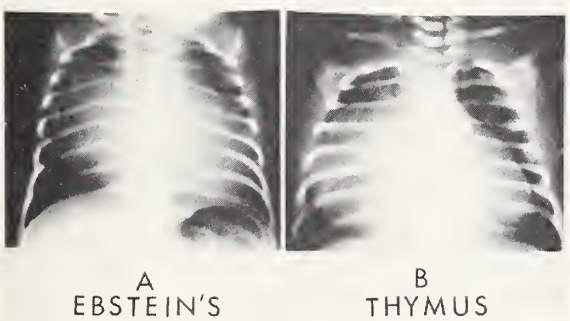


Figure 2.—Enlargement of thymus can mimic cardiac enlargement. Both of the chest roentgenograms illustrated are from two-day-old babies. The patient whose x-ray film is on the left had Ebstein's anomaly and died at five days of age. The apparent enlargement of the cardiac silhouette of the roentgenogram on the right is due to thymic, not cardiac, enlargement which had totally regressed by six months of age.

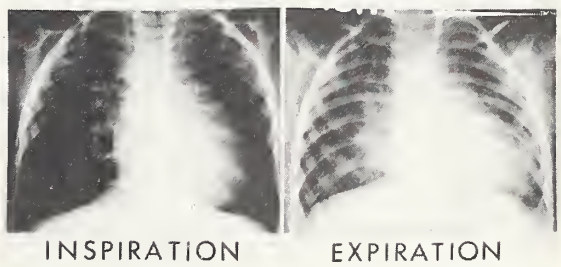


Figure 3.—The chest roentgenograms illustrated are both from the same patient who had "pink" tetralogy of Fallot and were taken within ten minutes of each other. The exposure on the left was taken during full inspiration and the exposure on the right during expiration.

*Origin of both great vessels from the right ventricle.

TABLE 2.—*Radiographic Diagnosis of Cardiovascular Disease in the Neonate*

PVM	Clinical Findings	EKG Findings	Diagnosis	CTD	MPA	Ao	Comments
▲	Cyanosis	RVH	HLH, MA	▲	►	▼	
			Trans.	▲	▼	►	"Eggshape"
			TAPVD	▲	▲	▼	"Snowman"
			TAPVD (below diaph.)	►	►	▼	
		LVH	TA (type C)	▲	►	►	
			HLH + VSD	▲	►	►	
		CVH†	SV	▲	▲	►	
			Truncus	▲	▼	▲	Ao. arch rt. (40%)[22]
	No cyanosis	RVH	ASD	▲	▲	►	Ao. arch rt.
		LVH	PDA	▲	►	▲	
			AP Window	▲	►	▲	
			AV Fist.	▲	►	►	
		CVH	VSD	▲	►	►	
			AV Com.	▲	►	►	
			AV Block	▲	►	►	
▼	Cyanosis	RVH	TOF	►	▼	▲	Ao. arch rt. (34%)[22]
			PS	▲	▲	►	Ao. arch lt.
		LVH	TA (type A)	►	▼	▲	Ao. arch rt. (10%)[22]
			PA	▲	►	►	
			Ebstein's	▲	►	▼	
►	No cyanosis	RVH	PI	▲	▲	►	
		LVH	Coarc.	▲	►	▲	
			AS	▲	►	▲	
			AI	▲	►	▲	
			MI, PMD	▲	►	►	LA ▲
		No VH	PAT	▲	►	►	
			Vas. Ring	►	►	►	Tracheal Compression[17]

*Active or passive.
†CVH or either RVH or LVH.

► Normal or no increase in size.
▲ Increased size or prominence.
▼ Diminished size or prominence.

LEGEND

AI=Aortic insufficiency; Ao=Aorta or aortic; AS=Aortic stenosis; ASD=Atrial septal defect; AP Window=Aortopulmonary window; AV Block=Atrioventricular heart block (Complete); AV Com.=Atrioventricularis communis; AV Fist.=Arteriovenous fistula; Coarc.=Coarctation of the aorta; CTD=Cardiac transverse diameter; CVH=Combined ventricular hypertrophy; Diaph.=Diaphragm; HLH=Hypoplasia of the left heart; LA=Left atrium; LVH=Left ventricular hypertrophy; MA=Mitral atresia; MI=Mitral insufficiency; MPA=Main pulmonary artery; PA=Pulmonary atresia; PAT=Paroxysmal atrial tachycardia; PDA=Patent ductus arteriosus; PI=Pulmonary insufficiency; PMD=Primary myocardial disease; PS=Pulmonary stenosis; PVM=Pulmonary vascular markings; RVH=Right ventricular hypertrophy; SV=Single ventricle; TA=Tricuspid atresia; TAPVD=Total anomalous pulmonary venous drainage; TOF=Tetralogy of Fallot; Trans.=Transposition of the great arteries; Vas. Ring=Vascular ring; VH=Ventricular hypertrophy; VSD=Ventricular septal defect.

Electrocardiogram

The electrocardiogram frequently is of limited value in the neonate since most of the serious cardiac lesions in this age group are associated with right ventricular hypertrophy and the differentiation of "normal" or "physiological" right ventricular hypertrophy from "abnormal" hypertrophy is often impossible (Figure 5). The criteria used at this hospital for "abnormal" right ventricular hypertrophy are listed in Table 3. A "normal adult pattern" in the neonate is pathognomonic of left ventricular hypertrophy (Figure 6). As illustrated in Figure 7, the electrocardiogram is usually of value in differentiating dextroposition, dextrocar-

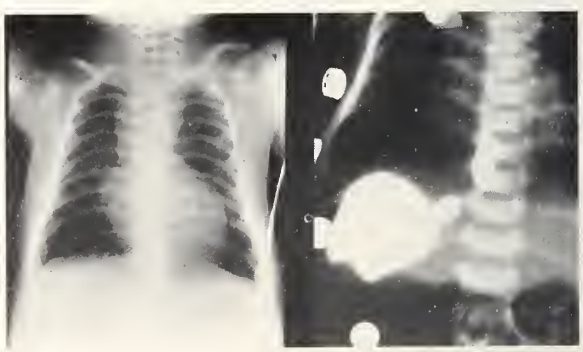


Figure 4.—Chest roentgenograms illustrating isolated levocardia. Notice that the gastric shadow is on the right while the cardiac shadow is on the left. The patient also had total anomalous pulmonary venous drainage below the diaphragm and tetralogy of Fallot.

TABLE 3.—*Electrocardiographic Criteria for "Abnormal" Right Ventricular Hypertrophy in the Neonate*

General Criteria	*Voltage Criteria*	*Intrinsicoid Deflection*
1. Frontal QRS axis $>180°$	1. $R_{AVR}>10$	1. Greater than 0.03 in V_1 (without IRBBB)
2. Pure R or qR in V_1	2. $R_{V_1}>20$	
3. R/S ratio in $V_1>90\%$		
4. Upright T wave in V_1 beyond 48 hours		
5. Depressed ST segment and deeply inverted T wave in V_1		

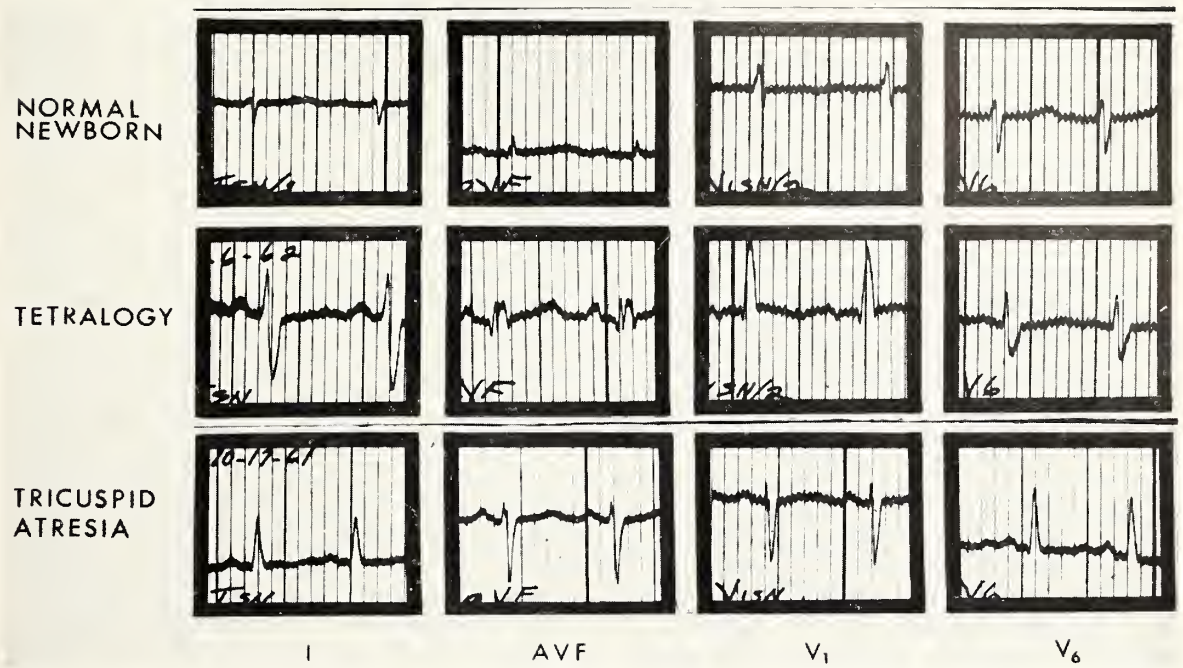


Figure 5.—The electrocardiogram of a normal newborn is compared with the tracing of a newborn with tetralogy of Fallot and a newborn with tricuspid atresia. The normal newborn tracing shows right ventricular dominance, similar to that of the newborn with tetralogy. The electrocardiogram of the neonate with tricuspid atresia is strikingly different showing left axis deviation and left ventricular dominance similar to an adult tracing.

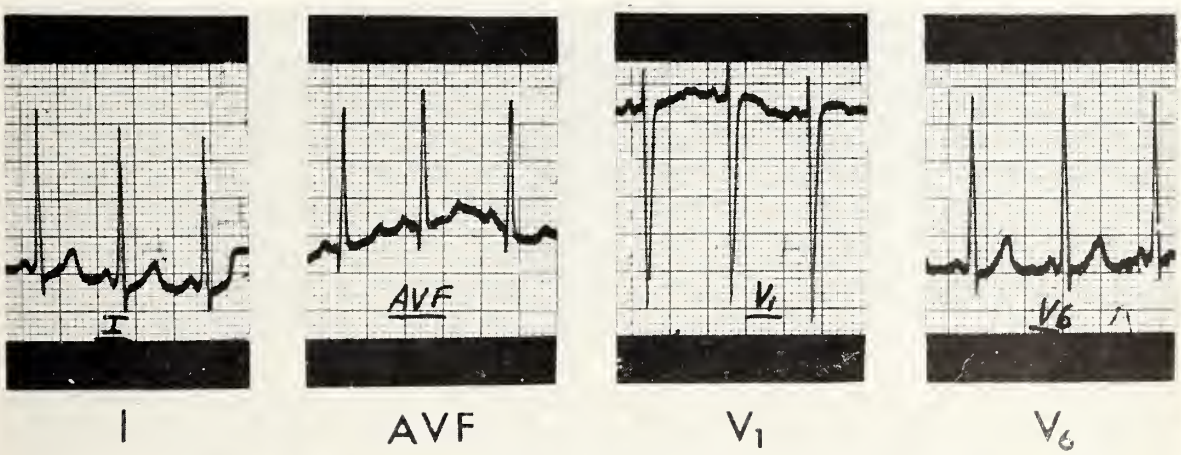


Figure 6.—A "normal adult" type electrocardiogram is always abnormal in a neonate. The tracing which is illustrated was obtained from a baby boy with single ventricle.

dia and dextroversion. The electrocardiogram is essential for the differential diagnosis of tachycardia, bradycardia and irregular rhythm and for the detection of abnormal depolarization patterns such as the Wolff-Parkinson-White syndrome (WPW).

Differential Diagnosis and What Can Be Done

In differential diagnosis it is important first to remember that heart lesions which are lethal during the neonatal period are quite different from those seen in older children. Lesions such as hypoplasia of the left heart (HLH), transposition of the great arteries, endocardial fibroelastosis, pulmonary atresia, mitral atresia, tricuspid atresia and truncus are common, not rare, causes of cardiac distress in the newborn. Table 4 lists in order of descending frequency the types of neonatal cardiovascular lesions seen at the Sutter Memorial Hospital during the four and one-fourth year period from September 1962 to January 1967. Of the total of 182 patients, 34 percent died during the first 12 weeks of life and 58 percent (35 of 61) of these deaths were due to the seven lesions listed above.

When using the classification of the seven lethal lesions (Table 1), the approach to the differential diagnosis is further simplified when it is remembered that over 90 percent of the causes of neonatal distress can be classified into only the first three pathophysiological groups: (1) Large left-to-right shunt, (2) Large right-to-left shunt and (3) Severe obstruction. The use of this pathophysiological classification in differential diagnosis is outlined in the following paragraphs.

Large left-to-right shunts. Pulmonary plethora on the chest roentgenogram is the tip-off to this group of lesions. The magnitude of the hemodynamic overload is dependent both on the size of the defect and the difference between pulmonary and systemic resistance — the lower the pulmonary resistance, the greater the left-to-right shunt. There may be cyanosis due to interference with gaseous exchange from pulmonary edema or due to associated venoarterial shunts, but the critical lesion is tremendous pulmonary flooding.

Uncomplicated left-to-right shunting lesions

TABLE 4.—*Incidence and Prognosis for Various Types of Cardiovascular Disease in the Newborn (Sutter Memorial Hospital September 1962 to January 1967)*

Lesions	*No.*	*Age at Onset of Signs* 1st wk.	2-6 wks.	7-12 wks.	*Cardiac Distress**	*Surgical Survivors*	*Medical Survivors*	*Spontaneous "Cure" (47 cases)*	*Deaths (in first 12 wks.)*
1. VSD	39	4	10	25	38%	3/3	36/36	51%	0
2. TOF	23	5	9	9	83%	3/4	14/19	. . .	6
3. PDA	15	5	4	6	74%	5/5	9/10	20%	1
4. PS	11	1	5	5	36%	1/1	10/10		0
5. HLH	7	6	1	0	100%	. .	0/7		7
6. Trans.	7	3	4	0	100%	2/5	0/2		5
7. AS	6	2	1	3	50%	1/2	4/4		1
8. EFE	6	2	2	2	100%	.	3/6	33%	3
9. PA	6	4	2	0	100%	0/3	0/3		6
10. SV	6	0	5	1	83%	2/3	1/3	. . .	3
11. ASD	5	1	3	1	80%	1/2	3/3	40%	1
12. AV Block	5	3	1	1	20%		4/5	. .	1
13. AV Com.	5	0	1	4	100%	1/2	1/3	20%	3
14. MA	5	3	2	0	100%	0/2	0/3		5
15. TAPVD	5	1	3	1	100%	0/1	3/4		2
16. Coarc., com.	4	0	2	2	100%	. .	2/4		2
17. Coarc., uncom.	4	0	2	2	50%	1/2	2/2		1
18. PAT	4	1	2	1	100%	. .	4/4	. . .	0
19. TA	4	1	2	1	100%	1/3	0/1		3
20. Vas. Ring	4	1	2	1	100%	4/4	. . .		0
21. Trans., incom.	3	2	1	0	100%	. .	0/3	. . .	3
22. Truncus	3	1	2	0	100%	0/1	0/2	. .	3
23. Misc.	5	2	2	1	100%	.	0/5	. .	5
Totals	182	48	68	66	72%	25/43	96/139	15%	61 (34%)

*Congestive failure or hypoxia.

LEGEND

AS=Aortic stenosis; ASD=Atrial septal defect; AV Block=Atrioventricular heart block (Complete); AV Communis=Atrioventricularis communis; Coarc., com.=Coarctation of the aorta, complicated; Coarc., uncom.=Coarctation of the aorta, uncomplicated; EFE=Endocardial fibroelastosis; HLH=Hypoplasia of the left heart; MA=Mitral atresia; Misc.=Miscellaneous; PA=Pulmonary atresia; PAT=Paroxysmal atrial tachycardia; PDA=Patent ductus arteriosus; PS=Pulmonary stenosis; SV=Single ventricle; TA=Tricuspid atresia; TAPVD=Total anomalous pulmonary venous drainage; TOF=Tetralogy of Fallot; Trans.=Transposition of the great arteries; Trans., incom.=Transposition, incomplete; Vas. Ring=Vascular ring; VSD=Ventricular septal defect.

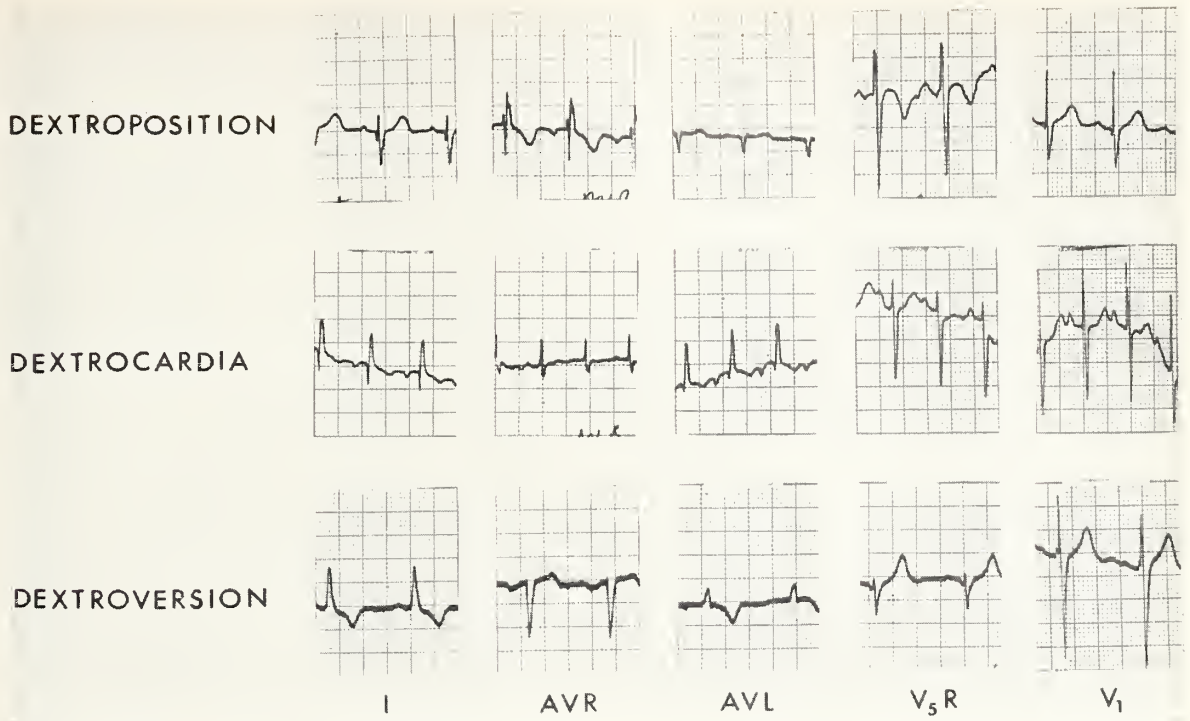


Figure 7.—Electrocardiographic differentiation of dextroposition, dextrocardia, and dextroversion is usually possible. The electrocardiogram in patients with dextroposition is normal except that the precordial transition zone is to the right. In mirror image dextrocardia both the P waves and T waves are inverted in Leads I and AVL and are upright in Lead AVR. In dextroversion only the T wave is inverted in Leads I and AVL and is upright in AVR.

usually do not cause significant symptoms until after the third week (Table 4). This late onset of distress is related to the relatively high pulmonary vascular resistance at birth. Conservative management is often indicated for patients in this category, particularly those with intracardiac shunts, due to the high neonatal surgical risk and the high percentage of lesions which undergo spontaneous closure (Table 4).

Since the clinical findings of ductus are usually atypical during the neonatal period and because the management and prognosis for ductus are so different from the other left-to-right shunting lesions, all patients in this group should be suspected to have ductus until proved not to by cardiac catheterization and angiography. These laboratory studies are therefore usually indicated early and often urgently in patients of this type.

Effective palliation can frequently be achieved by pulmonary artery banding in many of the other lesions associated with large left-to-right shunts[16] (ventricular septal defect, communis defect, aortopulmonary window, single ventricle, truncus, incomplete transposition, and tricuspid atresia type C[26]). Certain types of total anomalous pulmonary venous drainage can be corrected relatively easily by septoplasty.[40] The risk of corrective operation for the types of total anomalous pulmonary venous drainage which require transplantation of a common venous trunk is high and palliative atrial septectomy and pulmonary artery banding may be preferable.[5]

Neonatal congestive failure due to an uncomplicated atrial septal defect of the secundum type is rare. However, when there are progressive symptoms in spite of intensive medical therapy, open heart surgical correction of the defect is indicated and can be accomplished at relatively low risk.[34]

A large peripheral arteriovenous fistula, often intracranial or intrahepatic, can cause occult congestive failure and is occasionally diagnosed by the astute clinician who performs careful auscultation of the head and abdomen.[20]

Large right-to-left shunts. Sudden acute distress (hypercyanotic "spells") and severe metabolic acidosis due to anaerobic metabolism are common complications of these lesions.[44] Transposition of the great vessels is differentiated from the other types of severe cyanotic lesions by the presence of pulmonary plethora on the chest roentgenogram. Early atrial septectomy is mandatory for babies with transposition, not only to increase the arterial

saturation, but also to relieve pulmonary venous hypertension.[3]

Septectomy is best accomplished without thoracotomy by "popping" the atrial septum with a balloon (Rashkind) catheter[38] (Figure 8). A systemic pulmonary anastomosis (shunting procedure) of the Schumaker type[42] is the best approach to increase the pulmonary blood flow in patients with severe tetralogy and tricuspid atresia type A.[26] However, severely hypoplastic or aplastic pulmonary arteries may cause failure of shunts of any type. Use of the hyperbaric chamber seems to offer a significantly increased margin of safety in some of these babies.[2] Patients with uncomplicated severe valvar pulmonary stenosis can be improved at relatively low risk by pulmonary valvuloplasty, using hypothermia and inflow occlusion.[12]

There is at present no satisfactory treatment for pulmonary atresia. These patients are usually operated upon with the faint hope that a pulmonary valvotomy can be accomplished. Ebstein's anomaly of the tricuspid valve is usually not associated with hypoxia during the first few months of life. When there are progressive symptoms, a Glenn procedure (superior vena caval to right pulmonary artery anastomosis) may be life-saving but the risk is high.[47]

Severe Obstruction. The most common cause of death due to heart disease during the first week of life is hypoplasia of the left heart[35] (see Table 4). In this lesion the electrocardiogram shows right ventricular hypertrophy and the chest roentgenogram, pulmonary congestion. Patients with this condition all have pulmonary venous hypertension due to the absence of an adequate egress from the pulmonary veins or the left atrium or both, and they may also have systemic hypoperfusion due to an inadequate access route to the aorta or due to hypoplasia or aplasia of the ascending aorta and arch. When systemic hypoperfusion is present, the peripheral pulses usually cannot be felt and the flush blood pressure is below 40 mm of mercury.

Surprisingly, these babies usually appear normal at birth. This is, in part, owing to the fact that pulmonary flow and pulmonary venous pressure are low due to the persistence of the high fetal precapillary vascular resistance and to persistent patency of the ductus which provides an access route to the aorta from the right side of the heart. As the pulmonary vascular resistance falls, pulmonary blood flow, pulmonary venous volume and pulmonary venous pressure increase, resulting in a decreased pulmonary compliance and progressive dyspnea. Sudden vasoconstriction of the ductus may result in an acute "shock-like" clinical state which mimics the lethargic, ashen appearance of sepsis.

Most of these babies cannot be salvaged, but occasionally in those without systemic hypoperfusion, critical pulmonary venous hypertension can be relieved by atrial septectomy. In those with systemic hypoperfusion, when the aorta is of adequate size, there is experimental evidence to indicate that a Schumaker procedure[42] and distal banding of the pulmonary arteries may give effective palliation.[6] As there is no adequate egress from the left atrium, pulmonary venous hypertension is also



Figure 8.—Use of the Rashkind catheter allows for "non-surgical" creation of an atrial septal defect in patients with transposition of the great arteries. This procedure can usually be accomplished during diagnostic cardiac catheterization. The single frame from a cineangiogram on the left (A) illustrates the intact atrial septum during a left atrial cineangiogram. The middle frame (B) shows the balloon catheter inflated in the left atrium and the frame on the right (C) outlines the size of the atrial defect which was created after pulling the inflated balloon from the left atrium to the right atrium.

commonly the lethal physiological abnormality in patients with mitral atresia, as it is in patients with HLH, and an atrial septectomy may provide effective palliation.

Frequently single ventricle and transposition with or without pulmonary stenosis are associated with mitral atresia and the anatomical and clinical spectrum is broad. Aortic coarctation, characterized by strong axillary and absent or weak femoral pulses, is a common cause of distress after the first week of life (Table 4). When progressive failure occurs, cardiac catheterization is indicated to rule out complicating lesions. A preoperative aortogram is desirable for accurate identification of the location and length of the narrowed segment. Usually correction is possible by a relatively simple aortoplasty rather than resection and end-to-end anastomosis.[27] The clinical findings of critical uncomplicated valvar aortic stenosis are usually atypical during the neonatal period and there may be no systolic murmur. Observation of the negative contrast ejection stream from the left ventricle on the cineaortogram is a quick and effective way to establish this diagnosis.[7] Frequently there is complicating hypoplasia of the aortic annulus,[39] severely malformed valve leaflets or endocardial fibroelastosis,[23] and the salvage is consequently low. Aortic valve replacement has been successful in a few children but is technically very difficult in small infants.[43]

The problem of severe valvar pulmonary stenosis has been discussed previously under the cyanotic lesions. However, occasionally there are pronounced signs of right-sided failure when cyanosis is minimal or absent. Emergency valvotomy is lifesaving in such cases.[12] The hemodynamic handicap of patients with tricuspid atresia is occasionally accentuated by an inadequate egress from the right atrium. Creation of an atrial defect may be more important than changing the pulmonary blood flow by a shunting or banding procedure. The clinical picture of total anomalous pulmonary venous drainage below the diaphragm is completely different from drainage above the diaphragm, due to the fact that in the former there is pulmonary venous obstruction and hypertension. The heart is usually not enlarged and the chest roentgenogram shows pulmonary congestion.

Without operation these patients all die within six to eight weeks.[40] Total correction is difficult and dangerous. Experimental studies have shown that an atrial septectomy and distal pulmonary artery banding may provide effective palliation.[5]

Congenital mitral stenosis is rare and is usually associated with ductus and coarctation.[30] The diagnosis, even with cardiac catheterization and cineangiography, is difficult and must be differentiated from cor triatriatum and pulmonary venous obstruction. Surgical relief is rarely required during the neonatal period. Due to the pronounced deformity of the valve leaflets, relief usually requires replacement of the valve.

Primary Myocardial Disease (PMD). Endocardial fibroelastosis and myocarditis are the only common causes of primary myocardial disease during the neonatal period.[8] Accurate clinical differentiation of these two lesions is usually impossible. Both usually present a triad of massive cardiac enlargement (roentgenographically), progressive congestive failure, including gallop rhythm, and no significant murmur.

The electrocardiogram may show decided left ventricular hypertrophy and a "strain" pattern (Figure 9) suggesting endocardial fibroelastosis or there may be ST segment and T wave changes consistent with myocarditis.

Vigorous anticongestive therapy for both of these types of primary myocardial disease is indicated, but the salvage is low and persistent chronic failure is common.[28] Steroid therapy has been reported to be life-saving in some patients with myocarditis.[1]

Other forms of primary myocardial disease such as aberrant left coronary, glycogen storage disease, coronary vasculitis and idiopathic ventricular hypertrophy are rare and rarely cause symptoms during the neonatal period.

All patients with progressive distress from PMD should have angiographic visualization of the coronary arteries to rule out the surgically treatable lesion of aberrant left coronary and other potentially curable lesions which may mimic PMD. Congenital ventricular diverticulum is an extremely rare lesion which may mimic the clinical picture of PMD. The diagnosis can be made by palpation of the cardiac impulse in the epigastrium. Sudden rupture is common and salvage by early excision of the diverticulum is possible.[29] Acute distress from pericardial tamponade or constrictive pericardial disease is also rare in neonates but is usually occult and may masquerade as PMD. Recovery is possible if the disease is recognized and drainage and appropriate antimicrobial therapy instituted.[8,14]

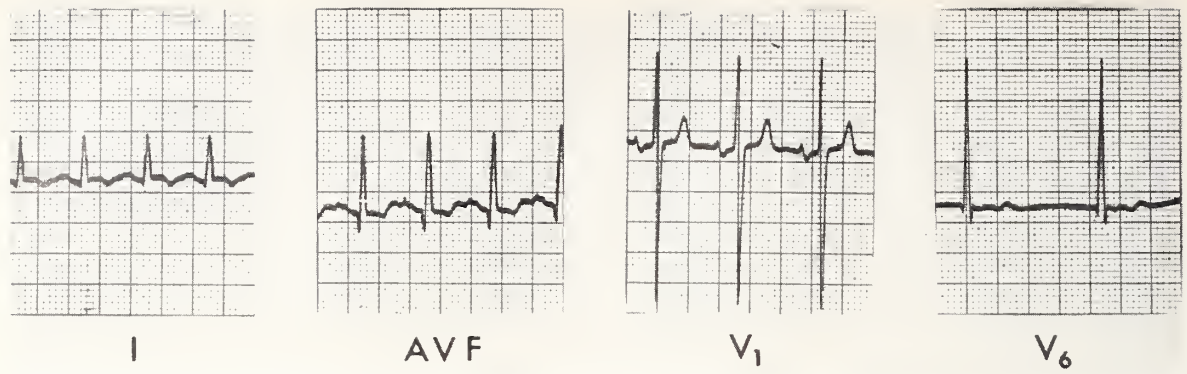


Figure 9.—The electrocardiogram, from a neonate who died of endocardial fibroelastosis, shows pronounced left ventricular hypertrophy and left ventricular "strain."

Massive Valvar Regurgitation. The regurgitant lesions are very rare and are included in this classification only for the sake of completeness. Isolated congenital valvar regurgitation is suspected from the unusual location (an apical systolic murmur with mitral insufficiency) or timing of the murmur (an early decrescendic diastolic murmur along the left sternal border with semilunar insufficiency) since apical murmurs and isolated semilunar insufficiency murmurs are infrequent in other types of neonatal cardiovascular disease.*

Patients with mitral insufficiency may have corrected transposition of the great vessels with Ebstein's anomaly of the left atrioventricular valve[41] or Marfan's syndrome. In the neonate, a loud aortic insufficiency murmur is usually due to a coronary fistula or a ruptured sinus of Valsalva rather than a regurgitant aortic valve.[18] Hemodynamically significant pulmonary insufficiency has also been reported in the newborn.[24] When there are progressive symptoms from a regurgitant lesion, surgical palliation by valvuloplasty or valve replacement is possible but the risk is high.[37]

Airway Obstruction. The neonate with a vascular ring most often first comes to medical attention because of a feeding problem, and formula changes are frequent before it is suspected that the stridor and dysphasia have a mechanical cause. The diagnosis is suspected on a routine chest roentgenogram by visualization of constriction of the negative tracheal shadow and by indentation of the esophagus following barium swallow. Cardiac catheterization and angiographic demonstration of the vessels involved are usually advisable (Figure 10). Correction should not be delayed, since a minor respiratory infection may suddenly accentuate the respiratory obstruction and result in sudden death. Following release of a vascular ring, stridor and symptoms similar to those of laryngotracheal malacia often persist for three to six months or longer. These residual symptoms may be related to persistent tracheobronchial changes which are secondary to the abnormal aerodynamics of the mechanical obstruction.

Arrhythmia. Paroxysmal atrial tachycardia is the most common arrhythmia during the neonatal period, and if it is not recognized death almost always ensues. The condition occurs mostly in boy babies and usually they do not have associated cardiac defects.[33] Reversion to sinus rhythm usually occurs within three to six hours following the beginning of digitalization. Occasionally reversion by electrical DC cardioversion is indicated.[36,45] Recur-



Figure 10.—Combined cineangiographic and barium swallow procedures demonstrate the vascular ring is due to a double aortic arch.

*The murmur of mitral insufficiency is heard in some patients with endocardial cushion defects and endocardial fibroelastosis. Semilunar insufficiency occurs in a small number of patients with ventricular septal defects when there is herniation of the non-coronary aortic cusp and in 10 to 25 percent of patients with truncus arteriosus.

rences are infrequent when maintenance digitalis is continued for six to twelve months. Ten to 20 percent of patients show WPW type conduction following reversion to sinus rhythm. Other forms of rapid heart beat, such as flutter and ventricular tachycardia, occur but are very rare. Analysis of the electrocardiogram is necessary for accurate differential diagnosis. The presence of apical clicks[21] and a variable intensity of the first sound[46] may be found in patients with ventricular tachycardia in contrast to those with supraventricular tachycardia.

Congenital complete heart block infrequently results in distress under two years of age unless there are associated cardiac anomalies causing significantly increased hemodynamic overloads. The first episode of cardiac arrest is rarely lethal and use of a pacemaker in children with uncomplicated heart block is not indicated until there have been two or more syncopal attacks. Heart block is more frequent in patients with corrected transposition of the great vessels.[41] Arrhythmias of all types are more frequent in patients with Ebstein's anomaly of the tricuspid valve.[32]

REFERENCES

1. Ainger, L. E.: Acute aseptic myocarditis: corticosteroid therapy, J. Pediat., 64:716, 1964.

2. Berhard, W. F.: Hyperbaric oxygenation, New Eng. J. Med., 271:562, 1964.

3. Bonham-Carter, R. E.: Congenital heart disease in the first six months of life, S.F. Heart Assoc. Symposium on Heart Disease, 2 Oct. 1963.

4. Cayler, G. G.: The management of heart disease in infants, J. Okla. St. Med. Assoc., 55:276, 1962.

5. Cayler, G. G.: Effective palliation for total anomalous pulmonary venous drainage: Clinical and experimental observations, In preparation.

6. Cayler, G. G.: Effective palliation for hypoplasia of the left heart (HLH) clinical and experimental observations, In preparation.

7. Cayler, G. G.: Congenital aortic stenosis: A correlation of the clinical and hemodynamic findings, In preparation.

8. Cayler, G. G.: Non-rheumatic inflammatory cardiovascular diseases, *In* F. H. Adams and A. J. Moss (Eds), Heart Disease in Infants, Children and Adolescents, Williams and Wilkins, Baltimore, Md., In publication.

9. Cayler, G. G.: Spontaneous closure of atrial septal defects, New Eng. J. Med., 276:65, 1967.

10. Cayler, G. G., and Smeloff, E. A.: The clinical diagnosis of congenital heart disease in children without recourse to expert auscultation, Medical Times, 93:74, 1965.

11. Cayler, G. G., and Smeloff, E. A.: Signs and symptoms of serious heart disease in the pediatric patient, Medical Times, 94:42, 1966.

12. Cayler, G. G., McFall, R. A., Yamauchi, T., Smeloff, E. A., and Cartwright, R. S.: Severe valvar pulmonary stenosis, Calif. Med., 101:44, 1964.

13. Cayler, G. G., Taybi, H., Richardson, W. R., Williams, G. R., Campbell, G. S., and Tassopoulos, N. M.: The "new" approach to the management of congenital heart disease in infants, Amer. Pract., 13:442, 1962.

14. Cayler, G. G., Taybi, H., Riley, H. D., and Simon, J. L.: Pericarditis with effusion in infants and children, J. Pediat., 63:264, 1963.

15. Cayler, G. G., Taybi, H., Tassopoulos, N. M., and Yamauchi, T.: An approach to the diagnosis of congenital heart disease in infants and children for the "non-cardiologist" physician, Medical Times, 91:423, 1963.

16. Cayler, G. G., Williams, G. R., Smeloff, E. A., Cartwright, R. S., Tassopoulos, N. M., and Carter, D. R.: Pulmonary artery banding in infants with cardiac anomalies other than ventricular septal defects, Dis. Chest, 47: 88, 1965.

17. Felson, B., and Palayew, M. J.: The two types of aortic arch, Radiology, 81:745, 1963.

18. Gasul, B. M., Aucilla, R. A., Fell, E. H., Lynfield, J., Bicoff, J. P., and Luan, L. L.: Congenital coronary arteriovenous fistula, Pediatrics, 25:531, 1960.

19. Gibson, S.: Eyes, hands and ears in the diagnosis of heart disease in children, Ped. Clin. N. Amer., 1:3, 1954.

20. Gomez, M. R., Whitten, C. F., Nolke, A., Bernstein, S., and Meyer, S. S.: Aneurysmal malformation of the great vein of Galen causing heart failure in early infancy, Pediatrics, 31:400, 1963.

21. Harvey, W. P., and Corrado, M. A.: Multiple sounds in paroxysmal ventricular tachycardia, New Eng. J. Med., 257:325, 1957.

22. Hastreiter, A. R., D'Crus, I. A., and Cantez, T.: Right-sided aorta, Brit. Heart J., 28:722, 1966.

23. Hastreiter, A. R., Oshima, M., Miller, R. A., Lev, M., and Paul, M. H.: Congenital aortic stenosis syndrome in infancy, Circulation, 28:1084, 1963.

24. Ho, T., Engle, M. A., and Holswade, G. R.: Congenital insufficiency of the pulmonic valve—A rare cause of neonatal heart failure, Pediatrics, 28:712, 1961.

25. Honick, G. L., Cayler, G. G., Williams, G. R., and Jacques, W. E.: Incomplete transposition of the great vessels (Taussig-Bing complex), Am. J. Cardiology, 10:149, 1962.

26. Keith, J. D., Rowe, R. P., and Vlad, P.: Heart Disease in Infancy and Childhood, Macmillan Co., New York, N.Y., 1958, p. 437.

27. King, H., and Waldhausen, J. A.: Aortoplasty in infants with coarctation, Circulation, 27:890, 1963.

28. Linde, L. M., and Adams, F. H.: Prognosis in endocardial fibroelastosis, AMA J. Dis. Child., 105:329, 1963.

29. Lowe, J. B., Williams, J. C. P., Robb, P., and Cole, D.: Congenital diverticulum of the left ventricle, Brit. Heart J., 21:101, 1959.

30. Lynch, M. F., Ryan, N. J., Williams, G. R., Cayler, G. G., Richardson, W. R., Campbell, G. S., and Taybi, H.: Preoperative diagnosis and surgical correction of supravalvar mitral stenosis and ventricular septal defect, Circulation, 25:854, 1962.

31. MacMahon, B., McKeown, T., and Record, R. G.: Incidence and life expectancy of children with congenital heart disease, Brit. Heart J., 15:121, 1953.

32. Mayer, F. E., Nadas, A. S., and Ongley, P. A.: Ebstein's anomaly, Circulation, 16:1057, 1957.

33. Nadas, A. S., Daescher, C. W., Roth, A., and Blumenthal, S. C.: Paroxysmal tachycardia in infants and children, Pediatrics, 9:167, 1952.

34. Nakamura, F. F., Hauck, A. S., and Nadas, A. S.: Atrial septal defects in infants, Pediatrics, 34:101, 1964.

35. Noonan, J. A., and Nadas, A. S.: The hypoplastic left heart syndrome: an analysis of 101 cases, Pediat. Clin. N. Amer., 5:1029, 1958.

36. Pryor, R., and Blount, S. G.: Refractory supraventricular tachycardia in infancy, AMA J. Dis. Child., 107: 428, 1964.

37. Puyau, F. A., Little, J. A., and Collins, H. A.: Mitral valve prosthesis in childhood, AMA J. Dis. Child., 108:651, 1964.

38. Rashkind, W. J., and Miller, W. W.: Creation of an atrial septal defect without thoractomy as a palliative approach to complete transposition of the great arteries, JAMA, 196:991, 1966.

39. Reeve, R., and Robinson, S. J.: Hypoplastic annulus—an unusual type of aortic stenosis, Dis. Chest, 45: 99, 1964.

40. Ryan, N. J., Williams, G. R., Cayler, G. G., Snyder, D. S., Taybi, H., Richardson, W. R., and Campbell, G. S.: Total anomalous pulmonary venous drainage, AMA J. Dis. Child., 105:76, 1963.

41. Scheibler, G. L., Edwards, J. E., Burchell, H. B., DuShane, J. W., Ongley, P. A., and Wood, E. H.: Congenital corrected transposition of the great vessels, Pediatrics, 27:851, 1961.

42. Shumacker, H. B., and Mendelbaum, I.: Ascending aortic-pulmonary artery shunts in cyanotic heart disease, Surgery, 52:675, 1962.

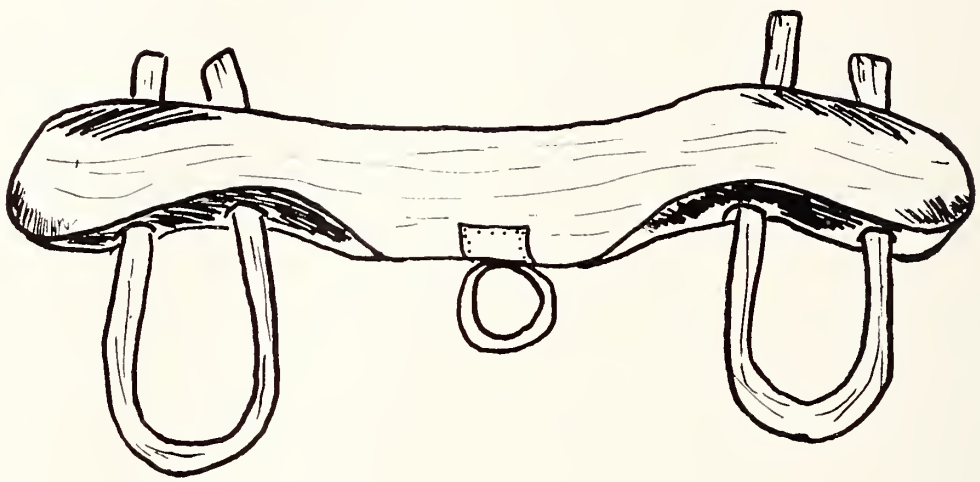
43. Smeloff, E. A., Cayler, G. G., and Smith, D. F.: The use of valve prostheses in children, J. Thorac. Cardiovas. Surg., 51:839, 1966.

44. Talner, N. S., and Ordway, N. K.: Acid-base balance in the newborn infant with congestive heart failure, Pediat. Clin. N. Amer., 13:983, 1966.

45. White, R. I., and Humphries, J. O.: Direct current electroshock in the treatment of supraventricular arrhythmias, J. Pediat., 70:119, 1967.

46. Wilson, W. S., Judge, R. D., and Siegal, J. H.: A simple diagnostic sign in ventricular tachycardia, New Eng. J. Med., 270:446, 1964.

47. Yamauchi, T., and Cayler, G. G.: Ebstein's anomaly in the neonate, AMA J. Dis. Child., 107:165, 1964.



Sacramento's Day-Treatment Center for Autistic Children

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■ *A report of two years' operation of a day-treatment center for autistic children is given. A brief historical review and a capsule summary regarding current concepts on autism are presented. The educational and treatment programs at the center are described, and two case vignettes illustrate the progress of the children. Highlights from group counseling sessions with the mothers of autistic children reveal the conflicts with which parents of disturbed children must deal. The two-year experience indicates that the identification of autism at an early age is crucial and that a day-treatment facility has much to offer the psychotic child and his parents.*

NEARLY A QUARTER of a century has passed since Kanner wrote his classic paper describing the baffling phenomenon of early infantile autism.[7] Despite the publication of many books and papers in the years since Kanner's discovery, few physicians are familiar with the syndrome, and fewer still have encountered it.

Briefly, Kanner delineated a group of psychotic children who manifested, from early developmental stages, emotional isolation from others (including parents), a pathological insistence on routine, and mutism or non-communicative speech. It is hard to convey the particular kind of heartbreak these afflicted children's non-response engenders in their bewildered parents.

Current Concepts

Theories about the causes of autism run the gamut from the psychogenic to the organic. Bettelheim's recent book presents the psychoanalytic case quite well.[2] On the organic front, Bender[1] argues that autism can be understood as a defense against central nervous system disorganization. Goldstein[4] holds that autism can be a manifestation of an inability to abstract because of brain damage. Rimland[11] suggests a genetic defect, centered in the reticular system.

Treatment methods have traditionally consisted of psychotherapeutic or psychopharmacologic approaches, or both. Recently, operant conditioning[8,9] and behavioral techniques have come to the fore. Fenichel[3] believes that the pathologic behavior is related to learning disorders and language handicaps, and he favors psycho-educational methods.

Before the existence of infantile and early childhood psychosis was recognized, the diagnosis was most often retardation and the patients were sent to large custodial institutions which offered no hope of recovery. As awareness grew, specialized

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residential treatment units, both public and private, came into being. In recent years, sparked by the efforts of small bands of parents, day-treatment centers have sprung up, usually on financially wobbly legs.

The Children's Center of Sacramento

In November 1965, Sacramento opened the only Northern California day-treatment center outside the San Francisco Bay area. The Children's Center of Sacramento is a private, non-profit facility for the treatment and education of mentally ill children. The immediate goal of the program is to so modify disordered thinking, feeling and behavior that the children will be able to "graduate" to a special education class, with the hope that ultimately they will be able to find a place in a normal school setting.

The Children's Center is licensed by the California Department of Mental Hygiene as a psychiatric treatment center for 15 ambulatory children, aged two to twelve years. Its physical plant is intended to resemble a home rather than a hospital, and it is in fact a remodeled ranchhouse. In addition to rooms devoted to general activity, play therapy, teaching, art and administration, there is a spacious outdoor play area, featuring the usual playground equipment, plus ample opportunity for sand and water play.

Staffing and Program

The board of directors consists of 18 members who are representatives of various professions and trades in the community. The staff includes a medical director who is a psychiatrist, an executive director representing psychology and special education, a psychiatric nurse, a psychiatric social worker, a special education teacher who is also a speech therapist, a child-care aide, and a corps of 18 volunteers who serve as additional child-care aides. These volunteers serve one or two days a week. A case conference is held on one child each week by the professional staff. A general staff meeting is held every day to discuss each child with regard to that day's activity and its significance to him.

The Center serves as a field training agency for Sacramento State College students from the departments of psychology, social work and special education. Not counting students and observers, the children relate themselves to a total of approximately 24 staff members, of whom only five are at the Center every day.

The program is planned and conducted as a nursery-kindergarten program with short sessions of academic basics as a child becomes able to tolerate structured learning. All of the children are in attendance from 9 a.m. till noon, and some of the older ones stay until 2 p.m. There are two structured group activities each morning — a half hour "snack time" and a half hour "circle time" (devoted to music, rhythms, story telling, or finger plays). There is no other "routine," and there is no set schedule for any child.

Some selected children are seen individually by members of the professional staff in a regular play therapy situation. Some are taught individually in the classroom by the special education teacher for periods as brief as ten minutes or as long as an hour. All are approached on an individual footing by all staff members, and if a child is responsive to someone, an attempt is made to build a relationship on that response. Every effort is made to effect flexibility and spontaneity. In this way, a child may spend an entire "school day" with only one person, and the following day spend only a brief time with that same person, according to the clinical judgment of the staff as to the child's relationship readiness and needs.

Group and individual activities emphasize socializing, body orientation and identification, eye contact, sense training, conceptual training and experiences. The training and education of these young children are very elementary, and basic to pre-school behavior patterns. The staff attempts to define limits of acceptable social behavior without denying these sick children full expression of pent-up feeling.

The academic education, for the most part pre-academic, consists of building basic concepts (sameness, differences, temperature awareness, tastes, smells and space orientation). Most of the "teaching" of the young children is concerned with developmental patterns which come naturally to normal pre-school children.

Parental Counseling

Since the children live at home, involvement of their parents in the therapeutic process is of extreme importance. Regrettably, because of staff shortages and time conflicts, the parents' group meetings have been extremely difficult to realize. For a one-year period, however, the mothers had

a weekly group meeting of an hour and a half with the social worker. The mothers expressed a need to confer on the ground that they had a mutuality of feelings as regarded their motherhood roles, and sensed deficiencies therein, although later in the sessions they were also to come to an awareness that what had also been operating was a search for a medium through which they could verbalize and look at some of their relationship problems with their husbands.

Group Process

The tone of the early meetings was set by immediate verbalizations of the mothers' needs to lean on each other, to talk to "someone" and, further, to have these talks under the auspices of the Center so as to have a professional person involved in their comparing of notes about their troubled children and their own feelings regarding them, and to thrash out ways of coping with their children and their problems more effectively.

From the expression of feelings in these early meetings it was apparent that the mothers were hungry for peer relationships and oppressed by a feeling that they and their children were different from and unwelcomed by families in their neighborhoods. Members of the group went on then to reveal their unhappy and "poor mother" self images to each other and to the group leader. The question of "Why my child?" which the group then began to face was a threatening one, and the social worker was asked to advance theoretical material in what was seen as the mothers' attempts to designate reasons which were beyond themselves. This phase was looked upon as a period of resistance in which the mothers were struggling against making overt that which they covertly felt — that is, that they were somehow involved in their children's disturbed emotional lives. Intellectualization was seen as the primary defense, and, as this was recognized and the fears behind it generalized by the social worker, the mothers moved into the area of expressing burdening guilt feelings regarding what each feared she had "done to my child."

Results of Group Counseling

As the year's time covered by this report was coming to an end, there was a substantial beginning on the part of several mothers toward recognizing, with their husbands, that neither "my fault" nor "your fault" was a complete answer, but that questions of role and relationship played a vital part in the family distress. No longer were the children seen as the entire focus, and some of the mothers were able to view themselves as related helpfully to their children as well as in the hurtful ways they feared. They seemed to be better able to use their energies to attend to and cope with the child behind the symptom, and to address themselves to marital relationship dilemmas.

Besides the group gains, there were instances of individual growth and movement, but these were seen as a limited kind of therapeutic experience. Most of the mothers were recognized as needing individual treatment or conjoint therapy with their husbands, or both. At present, treatment of this kind cannot be provided by the Center.

Progress of the Children

The children's progress has been highly variable. Only two of those who are there now have been at the Center the entire two years. Of six children who have left the program, two have been "successes" (as measured by achieving the ability to communicate more effectively, to attend public school in regular or special classrooms and to achieve the expression of appropriate emotional and behavioral responses to peers and adults); two are "failures" (ultimately requiring institutionalization); and two are regarded as having received limited benefit. Not all the children have been exclusively autistic. Practical considerations precluded any such selectional purism. In fact, as most investigators have found, severely disturbed children present a hodgepodge of organic, autistic and neurotic clinical features, and to a certain extent labels are academic.

Drug treatment has been essentially disappointing. The phenothiazines have proven of value in modifying hyperactivity and aggressive behavior, though they do not have the "antipsychotic" effect seen with adult patients. The "energizers" — the amphetamines and nicotinic acid, among others — have been of little help.

Some children are extremely refractory to treatment, and the staff may react with frustration and discouragement at their failure to progress. Others show spectacular improvement. One child was mute except for a garbled and indiscriminate "Mama" and "Daddy" when treatment began at age four and a half. A pediatrician had diagnosed "infantile autism, with severe mental retardation." In less than two years, the patient was speaking

complicated sentences. Recently he was expressing fear about the absence of parental love. A staff member attempted to give reassurance by saying that love is constant. "Oh, no," the child said: "It can go on and off like a light switch."

Most of the children show slow, irregular but definite improvement. Another patient, diagnosed by his attending physician as "retarded, probably neurologically handicapped," on admission showed echolalia, phobias of near panic proportions (regarding ordinary play activities and all people), and ritualistic behavior. In 21 months of treatment, rituals and parroting greatly diminished, and the child has conquered his fears to the point of attending the State Fair and loudly enjoying some of the more daring adult carnival rides.

Early Diagnosis and Treatment

Thus far there is a distinct impression that the younger the child when he comes to the Center, the better the prognosis. If this is a valid assumption, this characteristic of autism can be likened to the situation found in other disorders (for example, phenylketonuria, cretinism and rheumatic fever), in which the diagnosis must be made and treatment begun before a certain critical point has been reached if irreversible damage is to be prevented. This notion of there being a critical time during which autistic children must be reached is supported by the developmental phenomenon of "imprinting" in animals,[5] and by studies of feral children.[6]

Jean Piaget, the Swiss psychologist, has shown that the intellectual formation of the child proceeds according to innate stages of readiness.[10] Most teachers in elementary schools would agree with this, and would further agree that a child past the "reading readiness" age will have difficulty recovering that heightened potentiality. Such seems to be the case with autistic children relative to the basic ego and social skills of infancy and the preschool years. For this reason it is extremely important that infantile autism be recognized and treatment begun early. A greater awareness on the part of psychiatrists, general practitioners and pediatricians is needed.

Conclusion

The two years of operation of the Children's Center of Sacramento tends to support a cautiously optimistic view regarding the treatability and prognosis for autistic children. The enthusiastic staff of a small day-treatment center seems to have much to offer the autistic child and his parents. This impression agrees with the conclusion reached by Wenar and coworkers[12] in a recent study which demonstrated the superiority of a small day care unit emphasizing the emotional relationship between staff and children, compared with larger residential facilities offering custodial or therapeutic activity programs.

REFERENCES

1. Bender, L.: Autism in children with mental deficiency, Amer. J. Ment. Defic., 63:81-86, July 1959.

2. Bettelheim, B.: The Empty Fortress, Free Press, New York, 1967, pp. 385-423.

3. Fenichel, G.: Psycho-educational approaches for seriously disturbed children in the classroom, *in* Intervention Approaches in Educating Emotionally Disturbed Children, P. Knoblock, ed., Syracuse U. Press, Syracuse, N.Y., 1966, pp. 5-18.

4. Goldstein, K.: Abnormal conditions in infancy, J. Nerv. Ment. Dis., 128:538-557, June 1959.

5. Hess, E. H.: Imprinting, Science, 130:133-141, July 1959.

6. Itard, J. M. G.: The Wild Boy of Aveyron, Appleton-Century-Crofts, Inc., New York, 1962, pp. 55-101.

7. Kanner, L.: Early infantile autism, J. Pediatrics, 25: 211-217, Sept. 1944.

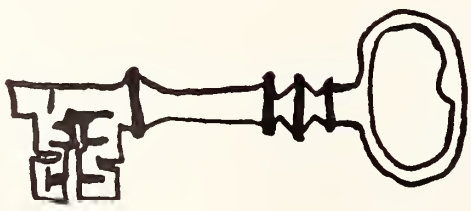
8. Lovaas, I., Freitag, G., and Kinder, M.: Establishment of social reinforcers in two schizophrenic children on the basis of food, J. Exp. Child Psychol., 4:109-25, Oct. 1966.

9. Lovaas, I., Berberich, J., Peiloff, B., and Schaffer, B.: Acquisition of imitative speech by schizophrenic children, Science, 151:705-707, Feb. 1966.

10. Piaget, J.: Language and Thought of the Child, Meridian, New York, 1955, pp. 25-170.

11. Rimland, B.: Infantile Autism, Appleton-Century-Crofts, Inc., New York, 1964, pp. 94-96.

12. Wenar, C., Ruttenberg, M., Dratman, N., and Wolf, E.: Changing autistic behavior, Arch. Gen. Psychiat., 17: 26-35, July 1967.



Cholesteatoma of the Ear

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■ *Cholesteatoma is a hazardous condition because of the erosion and tissue destruction, which result in deafness, and the complications which threaten life. Early diagnosis and treatment provide the best opportunity for eradication of the disease and preservation of hearing.*

The patient usually complains of intermittent or persistent ear drainage and of diminished hearing acuity. Close examination of the tympanic membrane reveals a perforation, which at times may be quite small, with epithelial extension into the middle ear space. In most instances surgical intervention is necessary for eradication of the disease.

CHOLESTEATOMA IS ONE of the most dangerous diseases involving the ear. It is dangerous because of its often insidious nature, often present a number of years before a serious complication occurs, and often goes unrecognized. The complications of cholesteatoma are of considerable magnitude, among them cerebral abscess, meningitis, lateral sinus thrombosis, facial paralysis and deafness.

Pathology

The disease is a result of the presence of squamous epithelium in the middle ear space or the mastoid process. There are at least two ways in which squamous epithelium gains access to these locations (where normally it is not present). One is by invagination of epithelium, usually in Shrapnell's area (pars flaccida), secondary to negative pressure in the middle ear space[2,4,5,6] (Figure 1). The other is by migration of epithelium through a tympanic membrane perforation.

Investigators also feel that desquamating epithelium may arise in the tympanum or mastoid as a result of epithelial cell arrest during embryological development[3,8] or as a result of metaplasia of the normal pavement epithelium of the epitympanic mucosa secondary to chronic infection.[5,6]

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Cholesteatoma of the ear, then, is a squamous epithelial-lined area (cavity) in the middle ear space or the mastoid or both. As the epithelium desquamates, there is no place for this material to go, and a cystic mass filled with debris is formed. The debris frequently contains crystals of cholesterol, hence the name cholesteatoma.

The presence of desquamated material in the moist crevices of the middle ear and mastoid cells provides an ideal medium for bacterial growth, so that the ear is usually chronically infected, although at certain stages it may be perfectly dry. Pressure necrosis and chronic osteitis result in progressive destruction of the areas involved. The destruction is slow and insidious; often there is a history of many years' duration. This is one of the dangerous aspects of the problem.

Both physicians and patients fall into the trap of reasoning that, since this has been a problem of many years and has not produced any serious complications, it probably never will. This is a false impression. Once the epithelium dissects into a cell or crevice and the infection becomes walled off by edematous mucosa or granulation tissue or debris, a potentially dangerous situation exists. The drainage is going to find a way out and if

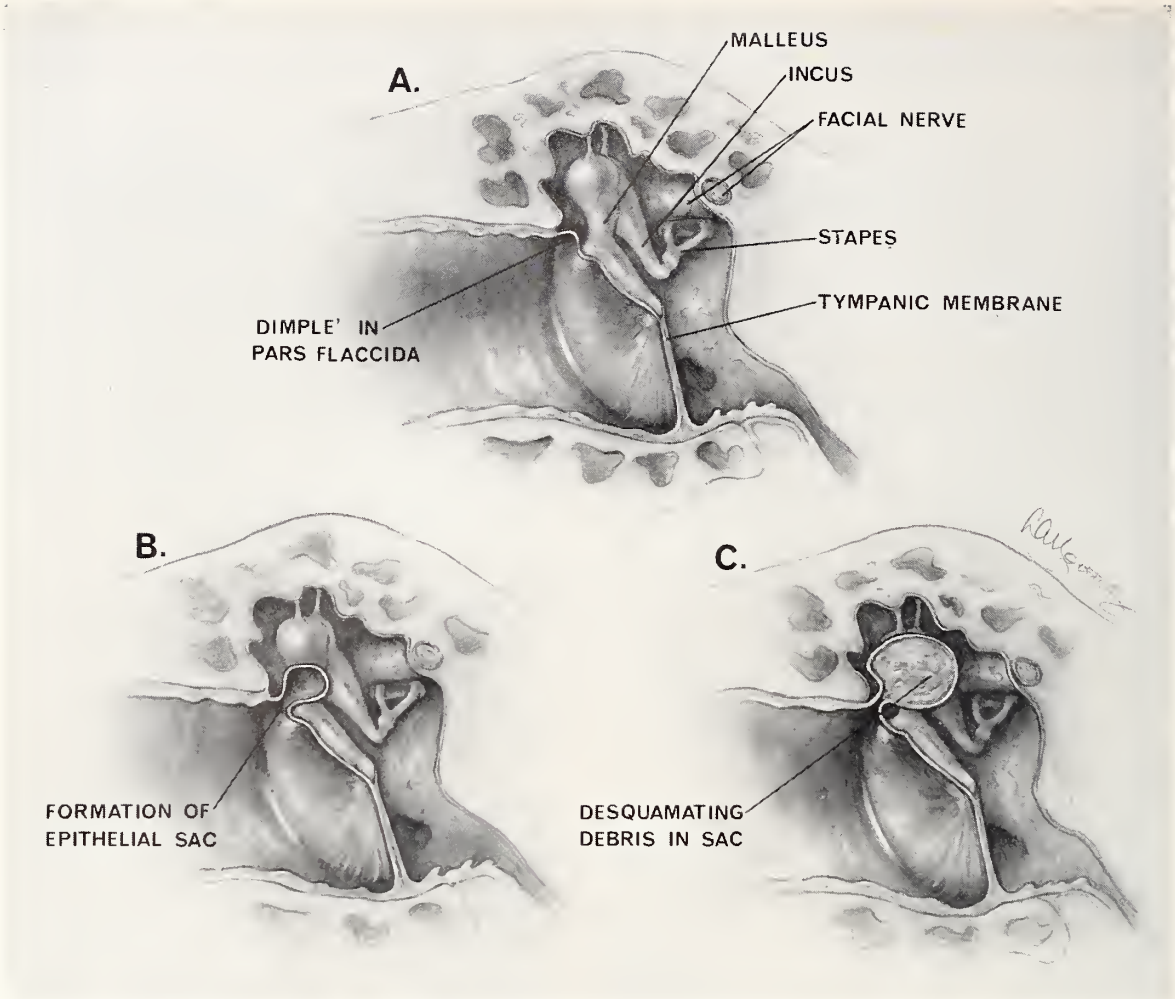


Figure 1.– Progressive stages in development of cholesteatoma secondary to invagination of pars flaccida.

emptied intracranially the result will be intracranial abscess, meningitis or lateral sinus thrombosis. Any of these complications is serious and a fatal outcome is common.

Facial paralysis may be the first sign to cause real alarm on the part of the patient or his physician. This complication is a result of osteitis or pressure necrosis involving the facial nerve as it courses through the temporal bone. Inflammatory swelling of the nerve occurs, and as the nerve is imbedded in a bony canal the swelling causes ischemia, with nerve damage and loss of function resulting.

Report of a Case

The patient, a 37-year-old man, was first seen in the office five years before the onset of the present illness. At that time he had inadvertently gotten water in his right ear while skiing and subsequently had had purulent drainage from it. The ear dried after a period of four months of intensive therapy. At that time, it was noted that there was a decided retraction in the epitympanic space, and the patient was advised of the necessity of continued close observation. Because there was no further drainage or pain, the patient did not return until, five years later, he was seen because of pain and drainage from the right ear of one week's duration.

Examination revealed an epitympanic perforation with epithelium extending posterosuperiorly (cholesteatoma). X-ray films of the mastoid area demonstrated an enlargement of the attic posteriorly, with poorly defined margins. Audiometric examination revealed a 30 decibel conductive hearing impairment. The patient was advised that surgical intervention would be necessary. Because of a previously scheduled vacation, he elected to

defer operation for several weeks, during which time he was to return at weekly intervals. Drug therapy was initiated and the drainage and pain began subsiding. However, on the second visit, a definite lid lag on the right side was noted. The patient had been unaware of this and had never had facial nerve weakness or neurologic symptoms at any time in the past. During the next two days a pronounced peripheral seventh nerve paresis developed, whereupon mastoidectomy was undertaken. At operation it was found that damage to the ossicular chain had destroyed the incus and a portion of the head of the malleus and had resulted in exposure of the horizontal portion of the facial nerve. Cholesteatoma and granulation tissue were completely excised, and with this eradication of the source of damage to the facial nerve it was felt that further decompression was not indicated. On the second postoperative day, the patient began to note an improvement in his facial function and by the time the dressing was removed a week after operation, recovery was almost complete. By the second week the facial nerve function was normal. At the end of six weeks the ear was dry and fully healed and hearing was at a satisfactory 15 decibel level.

Labyrinthitis with dizziness is not uncommon in cholesteatoma of the ear, especially during an acute exacerbation of chronic infection. Fortunately, this is usually due to irritative or serous labyrinthitis rather than to suppurative labyrinthitis, and usually the dizziness is not severe. The labyrinth becomes irritated due to its exposure as a result of cholesteatomatous destruction. There results a fistula of the semicircular canal and secondary labyrinthitis. Thrombophlebitic extension by way of the perilabyrinthine vascular system may also result in labyrinthitis.[1,7] If the irritative or serous labyrinthitis progresses to suppurative labyrinthitis, permanent total destruction of the sensory elements results, with total deafness and potential extension in the form of meningitis.

The extent and direction of destruction are unpredictable. In an occasional case the cholesteatoma brings about spontaneous radical "mastoidectomy," erosion having occurred into the auditory canal from the mastoid antrum. In others there may be only a tiny perforation in the epitympanic space and an otherwise normal appearing ear, yet the patient have one of the serious complications previously mentioned.

History and Examination

Cholesteatoma commonly is manifested by intermittent or persistent ear drainage and conductive hearing impairment. The hearing impairment will vary with the extent of the disease and, in early cholesteatoma, may be absent. As the chronic disease progresses, chronic osteitis and pressure necrosis will eventually disrupt the ossicular chain and finally progress to complete destruction with a minimum of 60-decibel hearing loss.

Pain may be a complaint if the infection becomes walled off by edematous mucosa or granulation tissue or if a secondary external otitis results from the purulent ear drainage.

Dizziness may occur intermittently. It is most likely to appear with cleaning of the ear during aspiration and, particularly, when a fistula into the semicircular canal has resulted from the destruction. Since applying positive and negative pressure with a pneumatic (Siegel's) otoscope will often produce nystagmus, the procedure is used as a diagnostic test. It is useful to the surgeon to know of the presence of a fistula preoperatively.

Detailed examination of the tympanic membrane is the critical point in diagnosis of cholesteatoma. Just looking at the light reflex is not adequate. The light reflex is often present in a cholesteatoma that is not infected and, in fact, the tympanic membrane may be quite normal in appearance. Shrapnell's membrane (pars flaccida) often holds the clue to danger. A severe retraction or perforation here almost always is accompanied by cholesteatoma to one degree or another. If there is only moderate retraction, danger of complications is minimal. One must see the innermost limits of the retracted sac, however, to be certain the cholesteatoma does not extend far beyond the confines of the area visualized. If the limits can be visualized, the lesion is of the type that can be safely watched without surgical intervention.

The second area that must be closely inspected is the posterosuperior quadrant of the tympanic membrane. Here a marginal perforation is a danger sign, for epithelium frequently will have migrated from the canal or tympanic membrane posterosuperiorly into the tympanum with progression into the mastoid additus and antrum.

Cholesteatoma can come about from central perforation but this is uncommon. Usually in such a case an atrophic retracted tympanic membrane has dropped into contact with the promontory of

the middle ear, allowing migration of the squamous epithelium into the middle ear space.

Cholesteatomas occasionally are found in patients with tympanic membranes intact. In these situations — far more frequent in children than adults — they are felt to be due to embryonic cell rests or to metaplasia of the epitympanic mucosa. The disease originally makes its appearance as resistant serous otitis media with conductive hearing impairment. Later, suppuration and destruction occur and findings are typical of cholesteatoma.

Unfortunately, information obtained from mastoid x-ray studies is frequently misleading unless extensive bone destruction has occurred. Tomograms will provide more detailed information, but even these studies may be misleading in early cholesteatoma, for at that stage there may be very little or no radiologically demonstrable bone destruction.

Examination of the ear under high magnification, therefore, is by far the most significant factor in the evaluation of cholesteatoma. This requires fastidious cleansing of the entire tympanic membrane and great care not to overlook even a small perforation which might be covered by a dried mucous crust especially in the region of the pars flaccida or in an atrophic retracted posterosuperior portion of the tympanic membrane.

Treatment

In most cases surgical intervention will be necessary to arrest the progress of the disease and preserve the patient's hearing. Sometimes, however, mechanical removal of the epithelial debris and having the patient avoid getting water in the ear will suffice, provided the extent of the epithelial extension into the epitympanic space or posteriorly into the tympanum can be determined with absolute certainty.

Not often is there need to operate immediately, but occasionally surgical intervention must be carried out as soon as a diagnosis is reached to prevent calamitous damage. (In the case herein reported, the patient could have had irreversible facial deformity had operation been delayed.)

The surgical approach is designed to eradicate the disease, thereby providing the patient with a safe, dry ear and preserving the hearing that is present. Reconstructive procedures may, in fact, improve hearing significantly, the degree depending upon the ossicular structures remaining. The earlier the diagnosis, the greater the opportunity for successful therapy.

REFERENCES

1. Bagby, R. A., and Farrior, J. B.: The treatment of the chronic middle ear in the pathogenesis of cholesteatoma, Southern Med. J., 46:712, July 1953.

2. Day, K. M.: Primary pseudocholesteatoma of the ear, Arch. Otolaryng., 34:1144, Dec. 1941.

3. McKenzie, D.: Pathogeny of aural cholesteatoma, J. Laryng., 46:163, Feb. 1931.

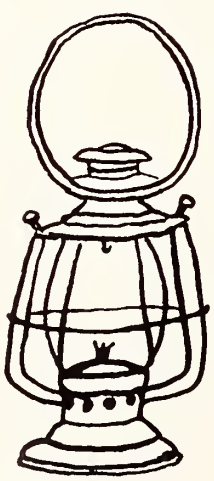
4. Nager, F.: The cholesteatoma of the middle ear, Ann. Otol., 34:1249, Dec. 1925.

5. Ruedi, L.: Pathogenesis and treatment of cholesteatoma in chronic suppuration of the temporal bone, Ann. Otol., 66:283, June 1957.

6. Saxen, A., and Ojala, L.: Pathogenesis of middle ear cholesteatoma arising from Shrapnell's membrane, Acta Oto-laryng., Suppl. 100, p. 33, Apr. 1952.

7. Shambaugh, G. E.: Surgery of the Ear, W. B. Saunders Co., Philadelphia, 1959, p. 162.

8. Teed, R. W.: Cholesteatoma verum tympani, Arch. Otolaryng., 24:455, Oct. 1936.



Fractures of the Calcaneus

Diagnosis and Treatment

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■ *Good lateral, Anthonsen oblique, anterior-posterior, and axial roentgenograms are necessary to define the extent of fractures of the calcaneus. Roentgenograms of the lumbar spine, including the thoracolumbar junction, are recommended whenever a fall has occurred sufficient to fracture the calcaneus.*

The great majority of calcaneal fractures are compression shearing fractures. Significant disruption of articular surfaces and spreading of the body beneath the fibula are major surgical problems and require careful treatment. In a series of 50 fractures treated by four methods, open reduction with stabilization by bone grafts, followed by active motion at six to eight weeks, gave the best results.

SUCCESSFUL TREATMENT of fractures of the calcaneus must begin with a positive attitude. One must not accept the cliché that comminuted calcaneal fractures usually require triple arthrodesis. A careful evaluation of the patient and of the type of fracture is required. Knowledge of the anatomy and function of the three components of the subtalar joint, the calcaneocuboid joint and the talonavicular joint, which sometimes has an associated subluxation, is, of course, essential to a reasonably accurate appraisal of the local problem.

Problems in Diagnosis

Such an appraisal is frequently difficult due to the problem in obtaining adequate roentgen visualization. Multiple projections, including the lateral, Anthonsen oblique, anterior-posterior and axial roentgenograms are essential for adequate analysis of the initial situation. A description of the positioning involved for the various roentgen projections has been described by a number of observers, including Wilson,[14] Thompson and Friesen,[12] and Warrick and Bremner.[13] Wilson pointed out the variation in the lateral roentgen projection between the position of inversion and eversion of the heel. The Anthonsen oblique usually brings out some details not clearly seen in the lateral, as has been noted by Schottstaedt[11] (See Figures 1 and 2).

Good details in the anterior-posterior projection reveal:

(1) The amount of lateral spread of the lateral fragments;

(2) Whether the calcaneocuboid joint is involved by fracture;

(3) Whether there is talonavicular subluxation (See Figure 3).

Good detail in the axial view shows the amount of lateral spread of the fractures and also the type

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of fractures involving the posterior calcaneal facet and sometimes the sustentaculum tali (Figure 4).

Additional fractures are frequently found at open operation despite the most careful preoperative roentgen examinations. Lumbar spine roentgenograms are taken routinely whether or not the patient has any low back complaints. This routine has been of great value in detecting mild compression fractures of the bodies of the lumbar and lower thoracic vertebrae (Figure 5). In addition, establishment of a baseline as to the presence or absence of degenerative disease of the spine, anomalies and the like has been very helpful in the evaluation of subsequent low back complaints which may have medicolegal implications.

Warrick and Bremner[13] developed an excellent atlas in color illustrating various types of calcaneal fracture. This atlas, of course, cannot be all-inclusive, for an infinite number of variations is possible. In addition, they classified three hundred fractures (Table 1). Figure 6, which was drawn using pictures in the Warrick and Bremner atlas



Figure 1.—Lateral view in case of fracture of calcaneus in 63-year-old man.



Figure 2.—Anthonsen oblique view (same patient as in Figure 1) bringing out details not seen in lateral view.



Figure 3.—Anterior-posterior view showing talonavicular subluxation.



Figure 4.—Axial view showing amount of lateral spread.

as models, illustrates the various kinds of fractures listed in Table 1.

Methods of Treatment

Obviously, the great range in the severity of the fractures with absence or presence of involvement of weight-bearing joints demands careful selection of treatment. Group 1 fractures may be treated initially by elevation, compression dressings and ice bags, followed by either active motion or protected weight-bearing in a few days if there are no other injuries. These fractures are usually no problem and frequently the patient may be treated in the office or as an out-patient.

Wide divergence of opinion exists as to treatment of Group II fractures. Methods of treatment that have been recommended for Group II calcaneal fractures are as follows:

- Conservative treatment as described above for Group I fractures.[1]
- Further comminution followed by molding as advocated by Cotton.[5]



Figure 5.—Lateral view of the spine at the thoracolumbar junction, such as should be included in all lumbar spine series.

- Various types of pin reduction, traction, and fixation techniques with or without early motion.[2,3]
- Primary manipulative reduction with skeletal traction followed in five weeks by triple arthrodesis.[4]
- Primary subtalar arthrodesis.[6]
- Primary triple arthrodesis.[12]
- Total excision of the calcaneus.[10]
- Open reduction with pin or screw fixation.
- Open reduction with bone grafts.[7,8,9]

Some light is shed on the problem by a careful consideration of each method of treatment. The goals of treatment should be a painless foot, nor-

TABLE I.—*Warrick and Bremner's[13] Classification of Fractures of the Calcaneus, Showing Incidence of Various Classes in a Series of 300 Cases.*

	Distribution of 300 fractures
Group I includes:	
Isolated fracture of the anterior end of the bone	40
Isolated fracture of the sustentaculum tali	1
Fracture of the tuberosity	
(1) "Beak" fracture 4	
(2) Vertical fracture 31	
35	35
Total Group I	76
Group II includes:	
A. Fractures with division of the bone into two main fragments only	
(1) Involving but not displacing the posterior articular facet	28
(2) Involving the posterior articular facet and accompanied by lateral displacement of the main lateral fragment	9
(3) With diminution of the tuber-joint angle but no involvement of the posterior articular facet	49
	86
B. Fracture with division of the bone into two main fragments and secondary compression fractures of the main lateral fragment	138
Total Group II	224
Fractures with displacement of the lateral part of the posterior articular facet were divided between Type 1* and Type 2 as follows:	
Type 1 63	
Type 2 34	
Total 97	
Fracture with displacement of the entire posterior articular facet were divided between Type 1 and Type 2 as follows:	
Type 1 23	
Type 2 18	
Total 41	

*Using Palmer's[9] classification of Group II fractures, Type 1 is defined as fractures with depression of that portion of the posterior articular facet lying lateral to the primary fracture. Type 2 is the type in which the depressed portion of the posterior articular facet is continuous with the upper part of the main lateral fragment which is split horizontally.

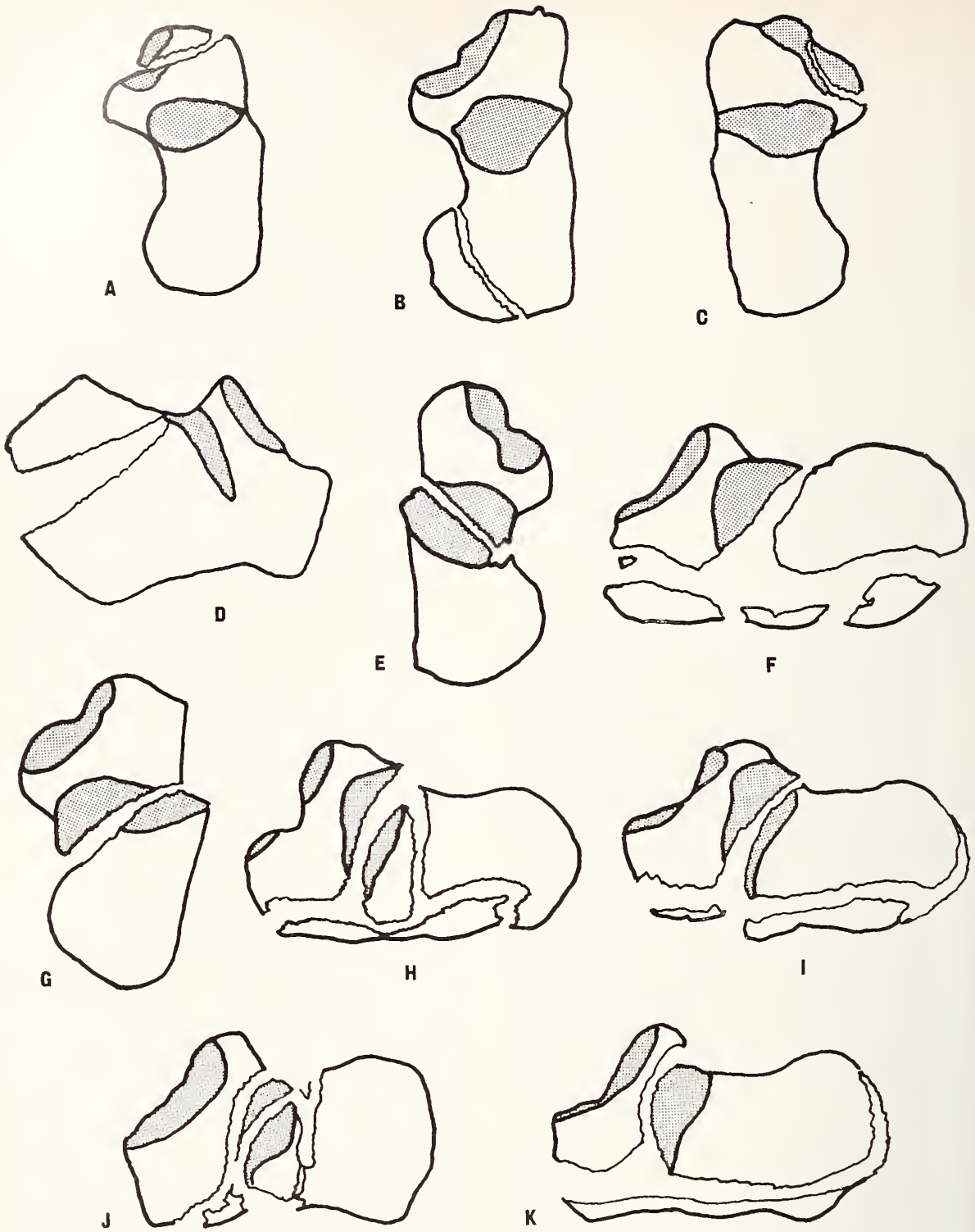


Figure 6.—Various kinds of fractures of the calcaneus. *A*, fracture of the anterior end of the bone involving the calcaneocuboid joint. *B*, vertical fracture of the tuberosity. *C*, isolated fracture of sustenaculum tali. *D*, "beak" fracture of the tuberosity. *E*, fracture involving but not displacing the posterior articular facet. *F*, fracture with diminution of the tuber-joint angle but no involvement of the posterior articular facet. *G*, fracture involving the posterior articular facet with lateral displacement of the main lateral fragment. *H*, fracture with depression of the lateral part of the articular surface (Type 1). *I*, fracture with depression of the lateral part of the articular surface (Type 2). *J*, fracture with depression of the entire posterior articular surface (Type 1). *K*, fracture with depression of the entire posterior articular surface (Type 2).

mal function of the subtalar, midtarsal and ankle joints, no deformity, and return to the former occupation within a reasonable time. An approximation of these goals requires the following treatment:

- Restoration of normal congruity of articular surfaces.
- Correction of the widening of the calcaneus beneath the lateral malleolus.
- Restoration of the normal tuber joint angle.
- Restoration of the height between the malleoli and the plantar surface of the heel pad.
- Commencement of active motion as soon as reasonable stability of the fractures has occurred.

Open Reduction with Bone Grafts

Undoubtedly, some Group II fractures may be treated conservatively with manipulation, casting or Steinman pin traction or fixation, with good results. However, achievement of the goals set forth above has appeared unlikely in Type 1, Group II fractures without open reduction and bone grafting. In addition, most Type 2, Group II fractures appear to be best handled in the same way. Therefore, the technique described by Palmer, with modifications, has been, for me, the treatment of choice. The following are the modifications of the Palmer technique as used by me:

- The incision is made to swing across the sinus tarsi from the lateral border of the long extensor tendons to just posterior to the lateral malleolus so as to allow better exposure of the subtalar joint and any projections of the fracture lines into the sustentaculum tali and calcaneocuboid joints. Care must be taken here to avoid the sural nerve.
- The peroneal sheaths are not opened but are dissected subperiosteally as an intact band of tendons with their sheaths, periosteum and fibular calcaneal ligament to prevent the tendency of the comminuted lateral wall of the calcaneus to spread out beneath the lateral malleolus after reduction. This lateral spread impinges on the peroneal tendons, squeezing them against the fibula so that ankle and subtalar motion is limited, and is the cause of persistent complaint of pain.
- Multiple segments of cortical and cancellous iliac bone, rather than a single block of bone, are firmly placed in the most appropriate planes to completely fill the defect caused by the impaction and to support the elevated articular surfaces. Experience has shown that recurrence of deformity is usually due to insertion of too little bone.

It is obvious that open reduction and bone grafting of calcaneus fractures are major procedures and should be performed only if there is significant displacement, and then by surgeons highly skilled in these methods and in hospitals well set up for these procedures.

The records of 47 patients with 50 fresh fractures of the calcaneus have been reviewed. All of the patients had their definitive treatment and most of them their follow-up care by the author. Methods of treatment of the 50 fractures were as follows:

- Casting 4
- Bohler type closed reduction with pin fixation 9
- Open reduction with excision of loose fragments and usually pin fixation 11
- Modified Palmer open reduction and bone grafting 26

The earliest method used in this series was of the Bohler type. Unsatisfactory results frequently occurred, requiring subtalar or triple arthrodesis to relieve subtalar and midtarsal arthritis. However, patients undergoing arthrodesis still had less than an ideal foot with not infrequent complaints of pain over the lateral heel and weakness of the foot and calf despite solid arthrodesis in optimal weight-bearing position. For example:

One patient, a 58-year-old man who had fallen about 15 feet onto his right foot about three months previously, had been treated elsewhere with a cast for seven weeks, and after three months still had complaint of pain in the lateral aspect of the right heel and in the sinus tarsi on walking. Protruding bone from the lateral border of the calcaneus and subtalar arthrodesis was excised, and films taken five months following operation showed clearly the residual shortening in length and height of the tuberosity, with resultant poor structure of the hind-foot. The patient returned to construction work almost 12 months after injury but was unable to walk backward carrying heavy forms. He still complained of pain over the lateral heel. (See Figures 7 and 8.)

Treatment in recent years of all significantly displaced Group II fractures has been by open reduction with bone grafts. Some details of management are as follows:

- No operation is done until the skin is free of blisters and abrasions. This usually requires seven



Figure 7.—Lateral and axial roentgenograms (case reported in text).

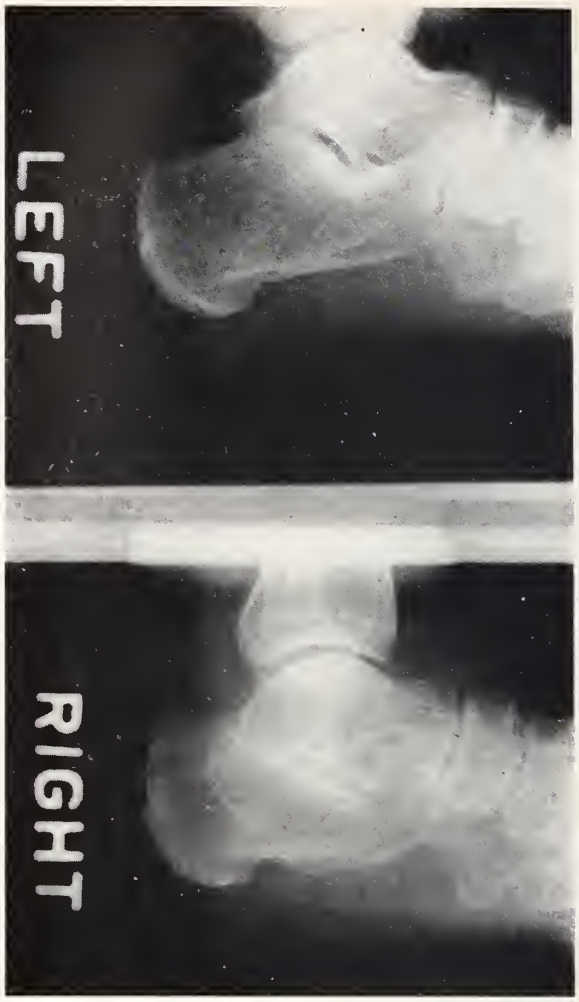


Figure 8.—(Same patient as in Figure 7.)—Lateral roentgenograms of left and right calcaneus after subtalar arthrodesis of right foot.

to ten days of elevation and application of ice bags or compresses.

- Postoperatively a pressure dressing, consisting a sterile sheet wadding and bias stockingette, is used, with an extra pressure pad beneath the fibula. A long leg cast is applied with the knee in moderate flexion and the ankle in about 10 degrees of equinus.
- The cast is removed at two weeks for removal of sutures and a new cast is applied.
- The cast is removed at six to eight weeks and active motion begun.
- Protected weight-bearing is started at 8 to 12 weeks.

At six months postoperatively most patients are pain free or subject to only relatively mild pain or ache on exertion. Ankle motion is excellent with rarely more than 5 degree impairment of full dorsiflexion and plantarflexion. Subtalar motion is usually limited with 25 percent to 50 percent of normal motion being considered very good and more than 50 percent of subtalar motion in both eversion and inversion being considered excellent. One patient was found to have fully normal subtalar motion, ten years after operation. Most patients have returned to their former occupations with little or no restriction of their activities. However, one roofer did not return to full duties as a roofer for three years. There were no deaths in this series and only two significant complications. In one patient with bilateral comminuted calcaneal fractures, pulmonary embolism developed, but recovery ensued. In one patient a low grade infection necessitated partial sequestrectomy. There has been no drainage from the heel in more than 16 years, but never was any subtalar motion regained.

REFERENCES

1. Barnard, Leonard: Non operative treatment of fractures of the calcaneus, J. Bone and Joint Surg., 45-A:865-867, June 1963.

2. Bohler, L.: Diagnosis, pathology and treatment of fractures of the os calcis, J. Bone and Joint Surg., 13:75-88, Jan. 1931.

3. Carothers, R. G., and Lyons, J. F.: Early mobilization in the treatment of os calcis fractures, Amer. J. Surg., 83:279-280, Mar. 1952.

4. Conn, H. R.: The treatment of fractures of the os calcis, J. Bone and Joint Surg., 17:392-405, Apr. 1935.

5. Cotton, F. J.: Os calcis fracture: Remodeling with mallet, Surg. Clin. N. Amer., 1:917-918, June 1921.

6. Hall, Michael C., and Pennal, George F.: Primary subtalar arthrodesis in the treatment of severe fractures of the calcaneum, J. Bone and Joint Surg., 42-B:336-343, May 1960.

7. Maxfield, Jack E., and McDermott, F. J.: Experiences with the Palmer open reduction of fractures of the calcaneus, J. Bone and Joint Surg., 37-A:99-106, Jan. 1955.

8. Maxfield, Jack E.: Treatment of calcaneal fractures by open reduction, J. Bone and Joint Surg., 45-A:868-871, June 1963.

9. Palmer, Ivar: The mechanism and treatment of fractures of the calcaneus. Open reduction with the use of cancellous grafts, J. Bone and Joint Surg., 30-A:2-8, Jan. 1948.

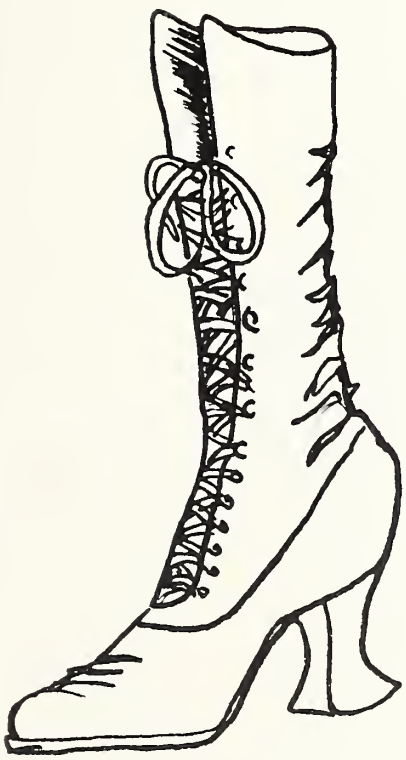
10. Pridie, K. H.: A new method of treatment for severe fractures of the os calcis. A preliminary report, Surg. Gynec. and Obstet., 82:671-675, June 1946.

11. Schottstaedt, Edwin R.: Symposium: Treatment of fractures of the calcaneus. Introduction, J. Bone and Joint Surg., 45-A:863-864, June 1963.

12. Thompson, Kearns R., and Friesen, Carl M.: Treatment of comminuted fractures of the calcaneus by primary triple arthrodesis, J. Bone and Joint Surg., 41-A: 1423-1436, Dec. 1959.

13. Warrick, C. K., and Bremner, A. E.: Fractures of the calcaneum, J. Bone and Joint Surg., 35-B:33-45, Feb. 1953.

14. Wilson, George E.: Fractures of the calcaneus, J. Bone and Joint Surg., 32-A:59-70, Jan. 1950.



School of Medicine

University of California, Davis

ACTIVE WORK TOWARD the establishment of a four-year curriculum in medicine at Davis began in February of 1966 with the arrival of C. J. Tupper, M.D., as Dean and Professor of Medicine. At that time, the dean was charged by Chancellor Emil M. Mrak with creating a four-year medical school at Davis as fast as possible, doing it efficiently, effectively, economically, with constant attention to excellence, and involving innovations in medical education.

The Dean and his faculty elected to simultaneously teach and build. Thus, they are in active construction of a "surge" campus to occupy until such time as permanent facilities become available, starting in the early 1970's. The surge facilities are Butler type, semi-prefabricated steel. A Health Sciences Library, occupied jointly with Veterinary Medicine, has been constructed and occupied, as has an initial faculty office and laboratory building. Active construction of student multidisciplinary teaching laboratories and additional faculty offices, lecture halls, and other supporting facilities is under way to provide space for teaching 48 entering medical students beginning 23 September 1968. The elapsed time, therefore, between the arrival of the Dean and the admission of students will be slightly over two and a half years.

The school, in preparing for admission of its first class, has received more than 1,500 requests for application materials and nearly 600 formal applications. Eighty-five percent of the applicants have been California residents. The incoming class has been selected and the caliber of students is considered by the admissions committee to be very high.

The faculty, which was seven in number by mid-1967, now totals 35 people on the scene with all basic science chairs filled, and a number of clinical chairs as well.

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The School of Medicine at Davis will provide students with a firm foundation of medical knowledge upon which they may develop a career in general or specialty practice, teaching, research, public health or administration. To accomplish this, an environment is being created that will attract students and faculty of excellence, that will provide maximum opportunity for the student to learn significant facts and principles, and that will enable and stimulate the student to develop intellectual inquiry and the self-discipline of responsibility for his own continuing education. The school and its faculty will strive to set by example the standards of clinical practice and responsible scientific inquiry that are the foundations of continuing professional competence.

The Dean and his faculty hold the position that medical schools can no longer afford the luxury of considering their responsibility completed with the awarding of the M.D. degree. They observe that 80 percent of the medical graduates in the United States go on to advanced training beyond the internship and hold that participation in this portion of medical education, as well as in the continuing education of the practicing physician, is an ever more clear responsibility of medical education.

The faculty is desirous of deemphasizing rigid departmental lines and for this reason has designed an interdisciplinary integrated curriculum. In addition, it plans introduction of clinical material from the outset. The artificial barriers between normal and abnormal, between basic and clinical, will similarly be deemphasized. The sciences basic to medicine will be presented in such a manner as to emphasize their relevance to clinical medicine. It is believed that such an approach will foster not only higher student motivation and performance but will at the same time provide the logical vehicle for learning medicine as a problem-solving discipline rather than a prodigious exercise in memorization and recall.

Upon enrolling in September, the medical students will stay in continuous enrollment for 15 consecutive quarters. The total contact time in a week will be approximately 20 hours. The remainder of the week will be unscheduled time that the student may use to take elective courses or in other ways that he deems most constructive in his studies.

The four-year program is organized into three core areas, plus "free time" during the first three years and a fourth year of electives chosen with faculty guidance. In the first year, referred to as Core A, four areas are included. These are: (1) molecular and cell biology; (2) organ and system biology; (3) introduction to clinical medicine; and (4) behavioral and environmental biology. In the behavioral and environmental biology course, attention will be given to psychological, sociologic, legal and economic problems concerned in medical care and in medical practice and attention will be given to the development of an awareness of the interaction of medicine and the community. The context of this course will also permit consideration of some of the significant literature related to the humanities in medicine.

The second year, or Core B, extends over four academic quarters totaling approximately 45 weeks. It will function around a patient problem-solving theme presented in the framework of organ systems. Specific clinical symptom-complexes have been selected for consideration in ten organ system areas as follows: (1) reproductive maturative; (2) neurodirectives; (3) chemodirectives; (4) hematopoietic-lymphoreticular; (5) cardiovascular; (6) respiratory; (7) urinary; (8) alimentary; (9) tegumentary; and (10) biomechanical-traumatic. Within each of these groups, the central problem of an abnormal clinical state (pathology) will be considered from the vantage points of the basic medical sciences and the medical and surgical specialties. Instruction in Core B will focus on the complaints of the patient presented live or through audiovisual aids, including moving pictures and videotapes. Laboratory studies will be directed toward exploration of underlying basic pathophysiology and rational therapeutic approaches. The introduction of physical diagnosis and history taking begun during Core A will be continued and expanded during this second year.

The third year, or Core C, comprises four academic quarters and provides expansion of experience with patients through clinical clerkships. Active exploration for the development of a method to allow students to follow a given patient from admission throughout his stay in hospital, including inter-service transfers and then follow-up after discharge from hospital, is under study, as are the logistic problems that are involved.

The fourth year of four quarters is to be made up of electives, or selectives, chosen with the guidance of the faculty advisor or preceptor. The activities within the year will be available at the school and at other institutions as well, where surrogate faculty members will be identified.

For the initial classes, the Sacramento County Hospital will represent the primary clinical resource. It is located 14 expressway miles from the Davis Campus and is a newly renovated 650-bed general facility. The permanent Medical Science Building on the Davis Campus is scheduled for occupation in 1973 and a 350-bed referral type University Hospital on the campus is scheduled for occupation in 1975. A continuing close affiliation with the Sacramento County Hospital, even after the University Hospital is available, is envisaged. It is also expected that a 740-bed Veterans Administration Hospital on the Davis Campus immediately adjacent to the University Hospital will be available. As these additional facilities come into use, the entering class size will be progressively increased to a planned maximum of 128 entering medical students. A full spectrum of residencies is under active development at the Sacramento County Hospital, with approved programs in general surgery, internal medicine and anesthesiology having been developed since the inception of the school, and many others are in active development.

Effective interaction in teaching and research between the School of Medicine and the School of Veterinary Medicine is already taking place and provides an exciting asset for the development of medical education at Davis, as do many of the other campus facilities, such as the National Center for Primate Biology, the Atomic Energy Commission-supported Radiobiology Laboratory, the new cyclotron, the Department of Nutrition and Animal Physiology in the School of Agriculture, and many others.

In spite of financial restrictions and limitations of space and equipment, the morale of the faculty is high and the Davis spirit of drive, momentum, and enthusiasm continues apace.

C. J. Tupper, M.D.

CASE REPORTS

Acute Necrotizing Encephalitis

Report of a Case Associated with Polycythemia Vera

GILBERT J. HUM, M.D., *Sacramento*

ACUTE NECROTIZING encephalitis is a form of encephalitis characterized by asymmetrical, and, in some cases, almost entirely unilateral cortical necrosis and inflammation with softening, edema or hemorrhage involving most frequently the temporal lobe and related rhinencephalic structures.[2,16]

Neurologic manifestations occur frequently in polycythemia vera.[25] Cerebral symptoms have been reported in from 5.6 percent[26] to 78 percent[27] of patients with this disease. One of the most common complications is intravascular thrombosis.[7,10,22,28] In a review of a series of 250 patients with polycythemia vera from 1933 to 1961, thrombosis was noted to be the cause of death in 100 (40 percent) and in 38 of the hundred the thrombosis was cerebral.[7] Seventy-nine patients (32 percent in the entire series) had cerebral thrombosis during the course of the disease.

The patient reported below had well-documented polycythemia vera and subsequently died of acute necrotizing encephalitis (ANE), showing combined encephalitis and necrosis. The case is being reported because of the relative rarity of ANE and the interesting, if not confusing, close clinical resemblance to a cerebral thrombotic complication. A brief review of ANE will be included and the possible relationship to polycythemia vera discussed.

From the Medical Service, Veterans Administration Hospital, Martinez.

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Report of a Case

A 64-year-old white man was admitted to the Oakland-Martinez Veterans Administration Hospital for the eighteenth time on 20 May 1964 because of loss of equilibrium, headaches, increasing confusion and inappropriate behavior of several days' duration. He had been observed at regular intervals since 13 October 1950, when a diagnosis of polycythemia vera was first established.

Over the ensuing years, phlebotomy was carried out a number of times and a total of 72.55 millicuries of P_{32} was given. Because of massive splenomegaly and leukocytosis up to 90,000 per cu mm. the patient was treated with busulfan, 2 to 6 mg daily, from 21 August 1962 to 6 April 1964, with good response. In addition, there were also complications of hyperuricemia, hyperuricosuria and recurrent renal calculi. Increased fluid intake, periodic alkalinization of the urine and administration of probenecid, 0.5 gm twice a day, were thought to control to some extent the formation of urinary calculi. The patient was last given 4.25 millicuries of P_{32} intravenously on 4 May 1964, and phlebotomy with removal of 500 ml of blood was performed on 7 May. When he was sent home on 11 May, his relatives noted loss of equilibrium.

Past history was not remarkable except for bilateral bronchopneumonia in 1962. There was no history of any other serious infection.

Physical Examination

On admission, the patient was intermittently confused and disoriented but in no acute distress. The temperature was 36.7° C (98° F.), pulse strong and regular at a rate of 82, blood pressure 110/64 mm of mercury and respirations 24 per minute. The pupils were small, but round, regular and equal and reacted to light and accommodation.

Extraocular movements were normal. There was a suggestion of left lower facial weakness. Deep tendon reflexes were hypoactive, but symmetrical and equal bilaterally. There was a flexor response to the Babinski test bilaterally and there was no clonus. Carotid pulsations were full and equal bilaterally. Conjunctivae were injected. Bilateral basilar crackling rales were present. The heart was not enlarged; cardiac rhythm was regular with a Grade I/VI blowing systolic murmur along the left sternal border. The spleen was quite firm and easily palpated 11.5 cm below the left costal margin along the midclavicular line. The liver was not felt and there was no peripheral edema, clubbing or cyanosis.

Laboratory Tests

Hemoglobin on admission was 16 gm per 100 ml, hematocrit 52 percent, erythrocytes 6.1 million per cu mm, leukocytes 33,900 per cu mm with 4 percent band forms, 88 percent neutrophils, 6 percent lymphocytes, 1 percent eosinophils and 1 percent basophils; platelets 408,000 per cu mm, and reticulocytes 1.2 percent. Uric acid was 9.1 mg, blood urea nitrogen 25 mg and fasting blood sugar 92 mg per 100 ml. An x-ray film of the chest showed slightly increased pulmonary markings and the electrocardiogram was borderline, with nonspecific ST segment and T-wave changes suggestive of digitalis effect.

Course

Spiking fever in the range of 38.9° C (102° F) rectally developed shortly after admission and the patient became increasingly confused, disoriented and lethargic. By the third hospital day, definite left hemiparesis had developed, with a Babinski sign on the left. His condition continued to deteriorate in spite of removal of 1,125 ml of blood during the first four days in hospital. By the fifth day, severe flaccid left hemiplegia was present with no field defect, sensory loss or aphasia. No foci of infection could be found to explain the fever and there was no response to antibiotics given empirically singly and in combination (penicillin, streptomycin, chloramphenicol, tetracycline). Blood cultures were repeatedly negative.

By 27 May the patient was intermittently semicomatose and responsive to his name and to painful stimuli. Neck stiffness had now developed. A lumbar puncture yielded clear, colorless cerebrospinal fluid. The opening pressure was 131 mm and the closing pressure 110 mm. The findings in the cerebrospinal fluid were as follows: 37 cells per cu mm, all lymphocytes; no red blood cells were seen; the sugar content was 72 mg, chlorides (NaCl) 730 mg and total protein 75 mg per 100 ml; globulin 3 plus. The result of a serological test for syphilis was negative.

The patient was comatose and unresponsive by 3 June and lumbar puncture was done again, with opening pressure of 150 mm and a closing pressure of 96 mm. The cerebrospinal fluid was again clear with 22 cells per cu mm, all lymphocytes; no red blood cells were seen. The findings in the cerebrospinal fluid at this time were: sugar 78 mg and total protein 31 mg per 100 ml; globulin 2 plus. India ink preparations and cultures for fungi and pyogens on both specimens of the cerebrospinal fluid were negative. On 11 June (22nd day in hospital) respirations increased to 40-48 per minute, flaccid paralysis developed on the right side, the temperature rose to 40.6° C (105° F) rectally and the patient died the following day.

Autopsy

At autopsy there was no evidence of systemic



Figure 1.—Frontal section of cerebral hemispheres at level of optic chiasm, thalamus and mamillary bodies, and of midbrain. Massive area of encephalomalacia with foci of hemorrhage is seen involving right basal ganglia and thalamus with smaller lesions in the tegmentum of the left midbrain.

vascular thrombosis or emboli. The lungs microscopically showed focal areas of bronchopneumonia. The liver weighed 2,200 gm and showed moderate central lobular congestion with some fat vacuolization of the central lobular cells. The spleen weighed 900 gm. There were intact Malpighian corpuscles, but the red pulp was devoid of red cells and showed numerous fusiform fibroblasts, as well as a prominence of littoral cells. The right kidney weighed 180 gm and was microscopically unremarkable. The left kidney weighed 100 gm and showed evidence of healed pyelonephritis. There was no evidence of renal calculi. Sections of the bone marrow from the sternum, femur, vertebrae and ribs were all similar, showing hypercellularity with a preponderant normoblastic hyperplasia.

The brain after fixation weighed 1,500 gm. It was symmetrical and showed only mild patchy atherosclerosis. The right hemisphere appeared swollen and tight, with compression of the sulci. There was uncal herniation bilaterally, greater on the left than the right. Coronal sections revealed an extensive lesion involving the entire basal ganglia on the right from a rostral level just anterior to the caudate nucleus down to the level of the thalamus (Figure 1). The lesion was fairly discrete and diffusely softened as a result of massive necrosis, with both yellow and red hemorrhagic foci scattered through it. It did not involve the adjacent insular cortex. It occluded partially the right lateral ventricle and caused a slight shift of the ventricle to the left. Two similar but small lesions were found in the anterior hypothalamus at the level of the anterior commissure on the left side, and in the anterior quadrigeminal body on the left side whence it partially extended into the adjacent tegmentum. All three lesions appeared to have no anatomical connection. There were also petechiae scattered through various parts of the cortex.

The three large lesions described grossly above and the small intracortical foci all had the same histological appearance (Figures 2 and 3). They consisted of central areas of massive necrosis with and without mobilization of gitter cells surrounded by peripheral zones in which gitter cells were intermingled with lymphocytes, disintegrating poly-

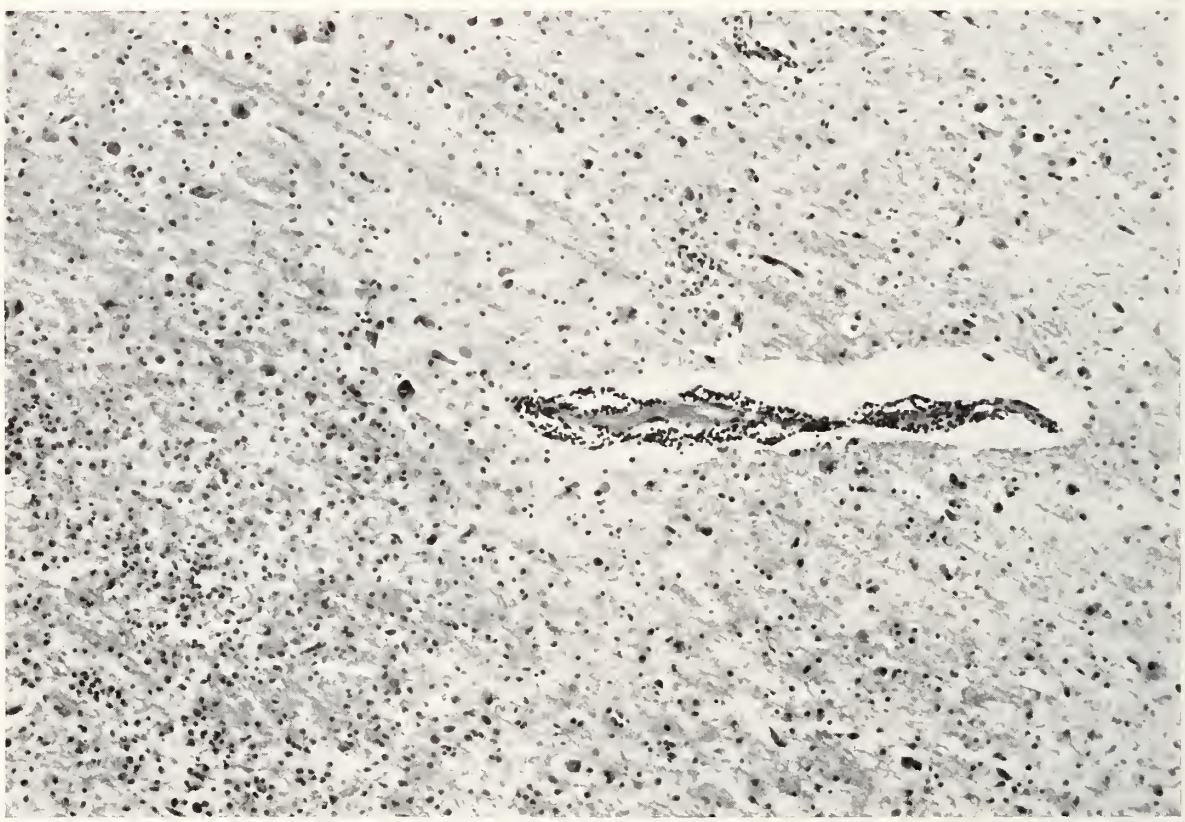


Figure 2.—Photomicrograph of portion of right basal ganglia showing perivascular lymphocytic infiltration, a finding noted in many areas, and in the lower left hand corner a focus of necrosis with polys, gitter cells and cellular debris intermixed. Hematoxylin and eosin; X100.

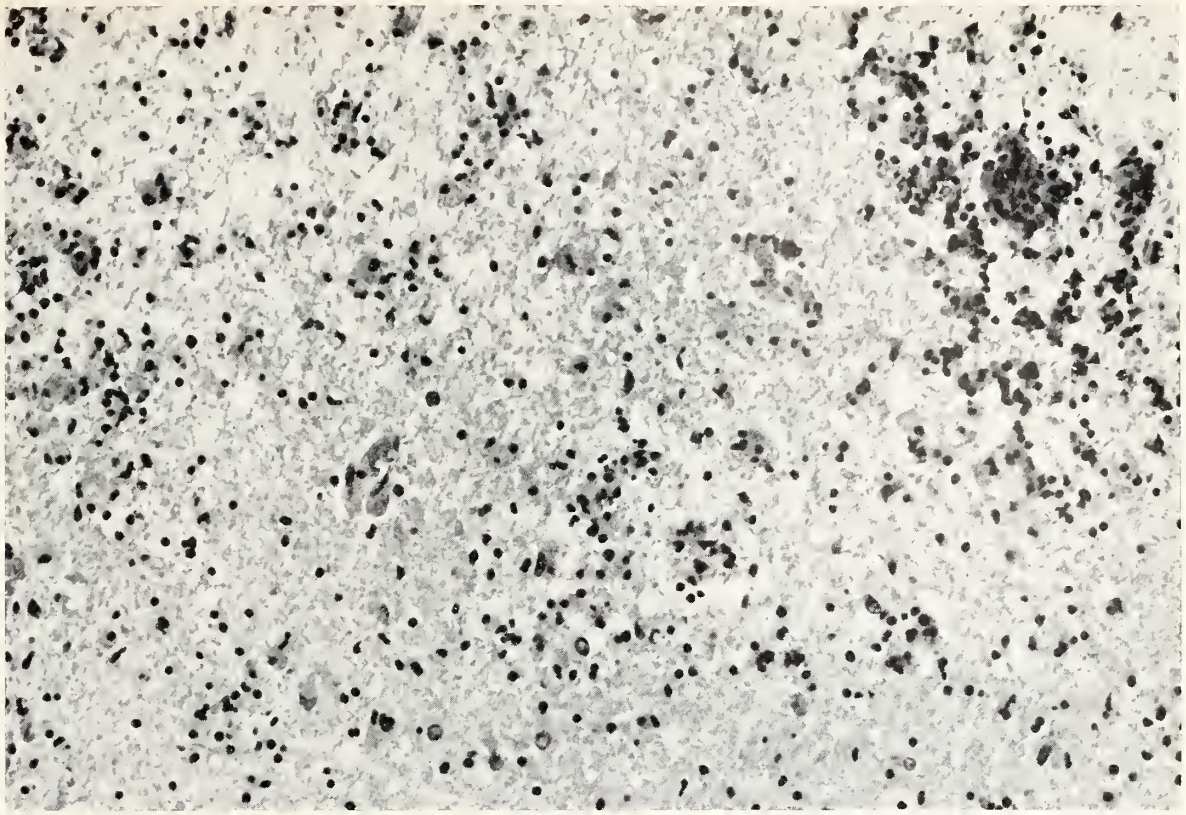


Figure 3.—Photomicrograph of a focal area of necrosis in the right cerebral cortex showing loss of structure and infiltration of lymphocytes, polys, and occasional gitter cells. Hematoxylin and eosin; X250.

morphonuclear leukocytes and proliferating astrocytes (Figure 4). There were no changes in the vessels supplying these areas. Within the necrotic zones, occasional blood vessels showed necrosis of the wall, thrombi, congestion and, rarely, perivascular hemorrhage.

In the intact nervous tissue about the lesions scattered microglial nodules and perivascular cuffing with lymphocytes were noted. In the rest of the brain there was no evidence of pathologic change beyond a mild lymphocytic meningitis.

Comment

The finding of pleocytosis was somewhat disturbing, but was finally ascribed to cerebral infarction and necrosis from the cerebral thrombosis.[8] The clinical course of an acute illness with progressive mental confusion, left hemiplegia and hyperthemia of presumably central origin correlated with the location of the lesion. Although the temporal lobe was not grossly involved, it was felt that the distinctive histological features with involvement of the anterior commissure, thalamus, hypothalamus, basal ganglia and cortex were consistent with the condition described as acute necrotizing encephalitis.

Discussion

It is beyond the scope of this report to discuss the problems and difficulties of classification and interpretation of the encephalitides. Cases heretofore reported as "herpes simplex encephalitis," "acute inclusion encephalitis," "acute inclusion encephalitis of the herpes simplex type," "acute necrotizing encephalitis with inclusions," "acute necrotizing hemorrhagic encephalitis" and "acute encephalitis with intranuclear cellular inclusions" are undoubtedly the same disease process.[2,5,11]

The most commonly associated or predisposing illnesses are nonspecific upper respiratory infection, sore throat and gastroenteritis. Fever is a characteristic of most of the reported cases, and mucocutaneous lesions were noted in some cases. The neurological signs and symptoms most commonly suggested diffuse neurological involvement, although in some cases focal neurological findings were present suggesting temporal lobe involvement.[2] Among other diseases considered in the

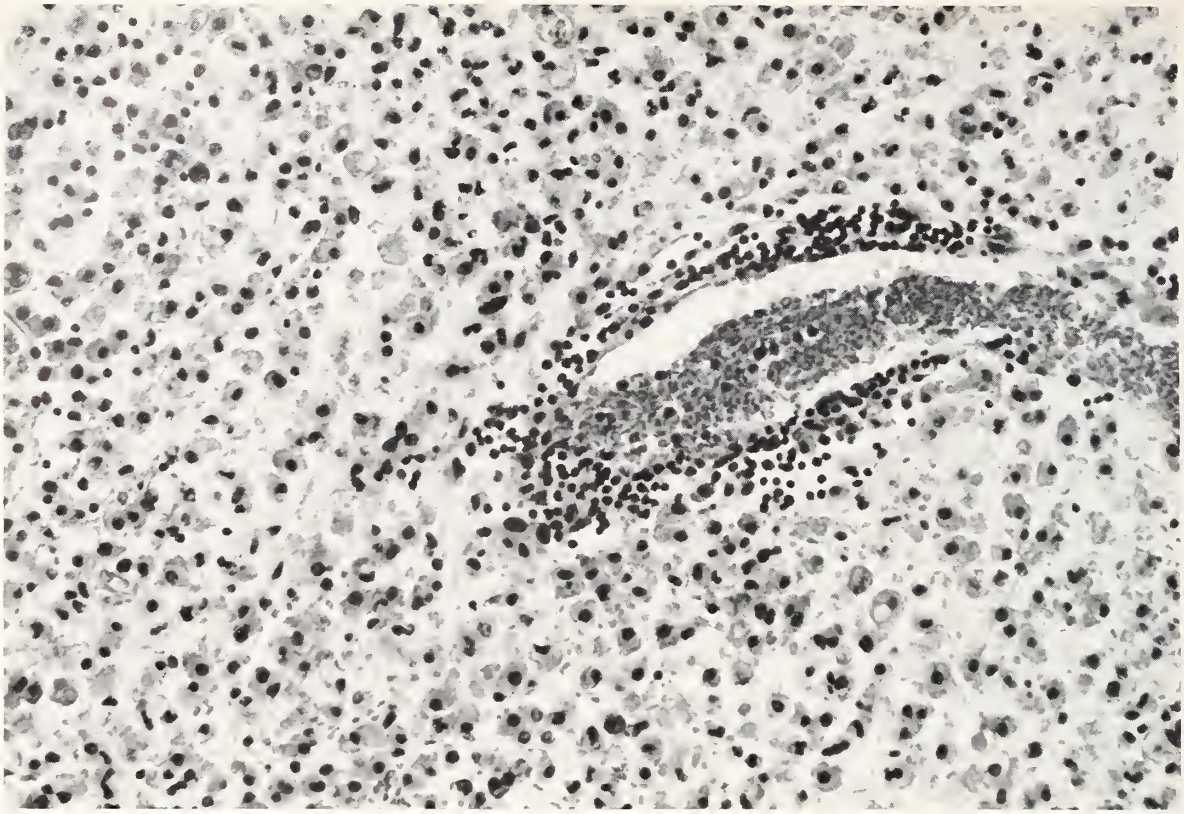


Figure 4.—Photomicrograph of the tegmentum of the left midbrain (lower portion of Figure 1), with a focal area of necrosis containing an extensive infiltration of gitter cells. Perivascular lymphocytic cuffing is well delineated. Hematoxylin and eosin; X250.

differential diagnosis in these conditions are intracerebral abscess, brain tumor, vascular malformations with hemorrhage, acute subdural hematoma and major vessel occlusion.

The diagnosis is rarely made antemortem[8] and indeed, as in the present case, it is not always even appreciated on examination of the fresh brain.[9] Surgical brain biopsy specimens may be misleading.[2,6] Pleocytosis of some degree is the usual finding.

Several recent reports have appeared discussing in some detail the differential diagnosis and clinical laboratory aids which would help establish a diagnosis antemortem.[5,12] Briefly, the diagnosis should be considered in patients who have signs of temporal lobe involvement in association with fever and mild pleocytosis of the cerebrospinal fluid, especially in the presence of mucocutaneous lesions and a history of recent or recurrent herpetic infection. Serological evidence of a recent herpes simplex infection is corroborative, but a fixed low-complement fixation titer during the acute stages of the illness does not exclude the diagnosis.[17] Equivocal complement-fixation tests were reported by Haymaker and coworkers[16] and Dodge and Curie.[11] In addition, the diagnosis of herpetic infections by serological methods is complicated by the demonstration of cross reactions in complement-fixation tests between herpes and varicella-zoster viruses.[24] In a report of 20 cases, Miller[20] emphasized the finding of otherwise unexplained erythrocytes in the spinal fluid, which was felt to reflect the hemorrhagic lesions that characterize herpetic encephalitis.

The pathologic findings corroborate the frequent temporal lobe signs and symptoms. The temporal lobe is the site most frequently involved, often unilaterally but, if bilaterally, with more severe involvement on one side than the other. Other sites frequently involved include the insular area of the frontal lobe, anterior part of the gyrus cinguli and the posterior orbital cortex.[16] Less commonly involved areas are structures of the anterior perforated substance, such as the ventral part of the septum pellucidum, subcallosal and paraolfactory gyri, anterior commissure (median part), and the nucleus accumbens septi, thalamus, hypothalamus, and basal ganglion.[2] Intranuclear inclusion bodies

have been found in some cases[2,12,15] and not in others.[8,9,14]

The cause of the disease is not clear. To date, herpes simplex virus has been the only definite organism identified, although it is not an invariable finding even when attempt is made to demonstrate its presence. Both Rawls[23] and Leider[19] suggest that herpes simplex encephalitis may be a localized recurrent manifestation of a latent herpes simplex infection. Electronmicroscopy in a case of suspected herpes simplex encephalitis reported by Itabashi and coworkers demonstrated viral particles in the inclusion bodies.[17] Moreover, serial serological tests have suggested that the etiological agent was herpes simplex.[11] Adams and coworkers,[1] in their report of three new cases of acute necrotizing encephalitis suggested the possibility that the disorder may represent a stereotyped reaction caused by more than one virus. On the other hand, Brihaye in 1958 stated that there was no conclusive evidence that acute necrotizing encephalitis was due to herpes simplex.

No known specific treatment is available. Early decompression to prevent irreversible damage from cerebral edema has been advised.[2,11] Trials with corticosteroids (cortisone and other related drugs) early in the course of the disease have been suggested.[5,18] In a recent clinicopathologic study of six cases, intravenous hydrocortisone was given in large doses to two patients, both of whom survived, although one other patient also survived without the use of hydrocortisone.[5] Administration of immune globulin was advised by Miller.[20] Two reports of improvement following systemic use of an analogue of thymidine, 5-iodo-2'deoxyuridine appeared recently,[3,13] although in one case the use was associated with decompression craniotomy. The mechanism is presumably interference with viral DNA synthesis.

To the best of our knowledge, there is no previous report in the literature of the coexistence of acute necrotizing encephalitis with polycythemia vera. In reported cases in which hematological values were given, there was nothing to suggest the concomitant presence of polycythemia vera. In many cases there was neutrophilic leukocytosis, which was attributed to the associated nonspecific upper respiratory infection or gastroenteritis.

Whether there is a causal relationship between polycythemia vera and acute necrotizing encephalitis or this is a coincidental occurrence cannot be answered on the basis of one isolated report. Susceptibility to infections is not one of the more frequently recognized complications of polycythemia vera. In one series of 250 patients who died with polycythemia vera,[7] death was directly attributed to an infection in 29 cases (8.4 percent); and in another series of 28 patients[4] infection was the cause of death in four cases (14.2 percent). The most common infections were bronchopneumonia and pyelonephritis. Since polycythemia vera may represent a neoplastic disorder it is possible that in some cases, such as that reported here, as in many other malignant diseases of the reticuloendothelial system[21] a state of relative immunologic unresponsiveness exists, resulting in a decreased resistance to infection, including herpes simplex infection.

Summary

A case of polycythemia vera complicated by clinically unsuspected acute necrotizing encephalitis is reported. The pathogenesis of acute necrotizing encephalitis is not clear, but herpes simplex infection of the central nervous system may be etiologically important. Treatment in previously reported cases included decompressive craniotomy, corticosteroids, immune globulin and, more recently, systemic 5-iodo-2'deoxyuridine. It is possible there is causal relationship between polycythemia vera and acute necrotizing encephalitis.

ACKNOWLEDGMENT. Nathan Malamud, M.D., Chief, Neuropathology Service, Langley Porter Neuropsychiatric Institute, San Francisco, permitted me to quote freely from his report of the gross pathological and histological findings of the brain.

REFERENCES

1. Adams, R. D., Berger, E. C., and van Bogaert, L.: Remarks on three new cases of acute necrotizing encephalitis, *In* Encephalitides—Proceeding of a Symposium on the Neuropath, Electroencephalography and Biochemistry of Encephalitides, Antwerp, 1959, Edited by van Bogaert, L., Radermecker, J., Hozay, J., and Lowenthal, A., Elsevier Publishing Company, 1961, pp. 266-282.

2. Bennett, D. R., Zurhein, G. M., and Roberts, T. S.: Acute necrotizing encephalitis. A diagnostic problem in temporal lobe disease: Report of 3 Cases, Arch. Neurol. 6:96-113, Feb. 1962.

3. Breeden, C., Hall, T., and Tyler, H.: Herpes simplex encephalitis treated with systemic 5-Iodo-2'deoxyuridine, Ann. Int. Med., 65:1050-1056, Nov. 1966.

4. Calabresi, P., and Meyer, O. O.: Polycythemia vera. II. Course and Therapy, Ann. Int. Med., 50:1203-1216, May 1959.

5. Carmon, A., Behar, A., and Beller, A. J.: Acute necrotizing hemorrhagic encephalitis presenting clinically as a space-occupying lesion. A clinicopathological study of six cases, J. Neurol. Sci., 2:328-343, July-Aug., 1965.

6. Case Records of the Massachusetts General Hospital, Case 61-1964, New Eng. J. Med., 271:1313-1320, 17 Dec. 1964.

7. Chievitz, E., and Thiede, T.: Complications and causes of death in polycythemia vera, Acta Med. Scand., 172:513-523, Nov. 1962.

8. Clinicopathological Conference: Acute necrotizing encephalitis, Marquette Medical Review, 30:133-140, May 1964.

9. Crawford, A. R., and Robinson, F. L. J.: Necrotizing encephalitis, Brain, 80:209-221, June 1967.

10. Dameshek, W.: Physiopathology and course of polycythemia vera as related to therapy, JAMA, 142:790-797, 18 Mar. 1950.

11. Dodge, P. R., and Curie, C. W.: Acute encephalitis with intranuclear cellular inclusions. A nonfatal case of probable herpetic etiology diagnosed by biopsy, New Eng. J. Med., 255:849-853, Nov. 1956.

12. Drachman, D. A., and Adams, R. D.: Herpes simplex and acute inclusion body encephalitis, Arch. Neurol., 7:45-63, July 1962.

13. Evans, A., Gray, O., Miller, M., Jones, E., Weeks, R., and Wells, C.: Herpes simplex virus encephalitis treated with idoxuridine, Brit. Med. J., 2:407-410, 13 May 1967.

14. Franken, L., Permentier, R., Kleyntjens, F., and van Bogaert, L.: Acute necrotizing encephalitis without inclusions, *In* Encephalitides—proceeding of a symposium on the Neuropath, Electroencephalography and Biochemistry of Encephalitides, Antwerp, 1959. Edited by van Bogaert, L., Radermecker, J., Hozay, J., and Lowenthal, A., Elsevier Publishing Company, 1961, pp. 243-252.

15. Haymaker, W.: Herpes simplex encephalitis in man, with a report of three cases, J. Neuropath. Exp. Neurol., 8:132-154, Apr. 1949.

16. Haymaker, W., Smith, M. G., van Bogaert, L., and de Chenar, C.: Pathology of viral disease in man characterized by nuclear inclusions with emphasis on herpes simplex and subacute inclusion encephalitis, *In* Viral Encephalitis. Edited by W. S. Fields and R. J. Blattner, 225 pp. Charles C Thomas, publisher, 1958, Springfield, Illinois, pp. 95-204.

17. Itabashi, H., Bass, D., and McCulloch, J.: Inclusion body of acute inclusion encephalitis: An electron-microscopic study in a case of suspected herpes simplex encephalitis, Arch. Neurol., 14:493-505, May 1966.

18. Lander, H.: Acute hemorrhagic leuko-encephalitis, Australasian Ann. Med., 7:55-68, Feb. 1958.

19. Leider, W., Magoffin, R., Lennett, E., and Leonards, L.: Herpes simplex virus encephalitis, New Eng. J. Med., 273-341-347, 12 Aug. 1965.

20. Miller, J., Hesser, F., and Tompkins, V.: Herpes simplex encephalitis, report of 20 cases, Ann. Int. Med., 64:92-103, Jan. 1966.

21. Miller, S. P., and Shanbrom, E.: Infectious syndromes of leukemias and lymphomas, Am. J. Med. Sci., 246:420-428, Oct. 1963.

22. Norman, I. L., and Allen, E. V.: The vascular complications of polycythemia, Amer. Heart J., 13:257-274, Mar. 1937.

23. Rawls, W., Dyck, P., Klass, D., Greer, III, H., and Herrmann, E.: Encephalitis associated with herpes simplex virus, Ann. Int. Med., 64:104-115, Jan. 1966.

24. Ross, C., and Sharpe, J.: Antigenic relationship of varicella-zoster and herpes simplex, Lancet, 2:708-711, 9 Oct. 1965.

25. Silverstein, A., Gilbert, H., and Wasserman, L.: Neurologic complications of polycythemia, Ann. Int. Med., 57:909-916, Dec. 1962.

26. Szur, L., Lewis, S., and Goolden, A.: Polycythemia vera and its treatment with radioactive phosphorus, Quart. J. Med., 28:397-424, July 1959.

27. Tenney, W., Hall, B., and Griffin, H.: Central nervous system manifestations and polycythemia vera, Proc. Mayo Clin., 18:300-303, 25 Aug. 1943.

28. Wasserman, L. R.: Polycythemia vera, its course and treatment, Bull. N.Y. Acad. Med., 30:343-375, May 1954.



MEDICAL STAFF CONFERENCE

The Clinical Spectrum of Fanconi's Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. RICHMOND*: An 18-year-old high school boy was admitted for the third time to the Moffitt Hospital on 17 December for general metabolic studies in the General Clinical Research Center. His present illness dates to the age of two when a routine urinalysis revealed proteinuria and hyaline casts. Although these findings persisted, other evidence of renal disease was not apparent. He grew and developed normally and was asymptomatic until age ten when he passed a single urinary stone. Because of the belief that this was a calcium stone, he was placed on, and faithfully followed, a diet containing neither milk nor dairy products. He remained asymptomatic until three years later, when he noted muscle spasm in his lower extremities with exercise and mild aches in his ankles and knees. Because of these complaints, he was admitted to the U.C. Medical Center in September of 1962 at the age of 13 years and 10 months.

There was no family history of renal disease, kidney stones, rickets or other bone diseases.

On physical examination the patient appeared well developed and healthy. He was in the 52nd percentile in height and the 30th percentile in weight. Bone tenderness was not demonstrable.

Significant laboratory studies at the time of his first admission included urinalysis which showed 3+ proteinuria, a trace of glycosuria and occasional hyaline casts. Electrolytes were completely within normal limits on three separate occasions. Calcium was 10.5 mg and phosphate 2.2 mg per 100 ml and alkaline phosphatase was 32 Shinowara-Jones-Rinehart (SJR) units. Urinary alpha amino nitrogen was 290 mg per 24 hours, (normal for his age and size 100 mg per 24 hours). Tubular reabsorption of phosphate was 74 percent (normal more than 90 percent). In response to an ammonium chloride load, the urine pH decreased to 5.1 and urinary excretion of titratable acid in ammonium rose to normal rates. Urine osmolality after 14 hours dehydration and 5 units of Pitressin was only 368 mOsm per kg of water (normal >700). X-ray films of the long bones were consistent with rickets. An intravenous pyelogram showed diffuse nephrocalcinosis. A diagnosis of Fanconi's syndrome was made, even though the patient was not runted as is usual in Fanconi's syndrome in children.

The patient was discharged on a regular diet without restriction of milk or dairy products, and he drank a quart of milk per day. He became asymptomatic within three weeks.

The patient was readmitted to the General Clinical Research Center in February of 1966 for reevaluation of his kidney and metabolic status. He

*Stewart S. Richmond, M.D., Intern in Medicine.

was asymptomatic at that time, and physical examination was unremarkable. An examination of the eye grounds with a slit lamp showed no evidence of cystine crystals. X-ray films revealed no evidence of rickets. Serum electrolytes were again normal except for phosphate, which ranged from 2.4 to 2.6 mg per 100 ml. Creatinine was slightly elevated at 1.29 to 1.47 mg per 100 ml, the alkaline phosphatase had decreased to a normal value of 5.5 SJR units. Urinary excretion of calcium was elevated above normal and ranged from 338 to 356 mg in 24 hours on a normal calcium intake. Urinary excretion of protein was 3.1 gm for 14 hours. Tubular reabsorption of phosphate ranged from 67 to 74 percent, a distinctly subnormal range in light of the reduced serum phosphate. With ammonium chloride loading, urinary pH again decreased to a normal value of 5.3 and urinary excretion of titratable acid and ammonium increased to normal rates.

The present admission was specifically for evaluation of the renal capacity for bicarbonate reabsorption, which will be discussed by Dr. Morris.

May we have the x-ray films, please.

DR. RUSSELL*[1]: Films of the distal tibia and fibula were obtained in September of 1962 when the patient was 14. The bones were slightly demineralized. There was widening of the cartilaginous plates between the metaphysis and epiphysis. The margins of the epiphysis were blurred and frayed, with slight cupping. An abdominal film demonstrated multiple small punctate calcifications scattered throughout both kidneys. The kidneys were slightly smaller than usual, particularly the left.

X-ray examination was carried out again in December 1966. The distal tibia and fibula were then entirely normal except for a very slight valgus angulation. An abdominal film again demonstrated small punctate calcifications with little interval change.

DR. SMITH*[2]: Thank you very much, Dr. Russell. We are very fortunate to have Dr. Curtis Morris to discuss this patient in whom he has been very interested. Dr. Morris has carried out some outstanding investigations on renal tubular dysfunction, in particular on mechanisms of urine acidification and the abnormalities which may occur in disease. He will summarize the general problem of renal tubular defects in the Fanconi syndrome.

DR. MORRIS*[3]: Fanconi's syndrome can be defined as a biochemical syndrome characterized by the triad of glucosuria, aminoaciduria and increased renal clearance of phosphate secondary to impaired renal tubular reabsorption of glucose, amino acids and phosphate. These three impairments implicate the proximal tubule and they were demonstrated in the patient presented today. Unlike the patient presented this morning, the usual patient with Fanconi's syndrome also has the hyperchloremic acidosis characteristic of a nonazotemic renal acidification defect. In some patients with Fanconi's syndrome, particularly those with Wilson's disease, hypouricemia occurs secondary to impaired renal tubular reabsorption of uric acid. Proteinuria of a rather special type occurs in patients with Fanconi's syndrome and other dysfunctions of the renal tubule. The protein excreted migrates electrophoretically like a "slow" globulin. Lysozymuria, the urinary excretion of lysozyme (a small molecular weight enzyme not demonstrable in the urine of normal persons), has been described recently in experimental and clinical Fanconi's syndrome and other renal disorders.

Fanconi's syndrome may be classified in five etiological categories: (1) idiopathic, (2) as a concomitant or integral part of a genetically transmitted disease, (3) medullary cystic disease, (4) acquired, and (5) experimental forms (Table 1). The Fanconi's syndrome of the patient presented today cannot be classified with certainty. He had no family history suggestive of Fanconi's syndrome, no history of exposure to an agent known to cause the disorder and no physical signs or laboratory evidence of cystinosis or other coexistent metabolic disorders. The findings of hypercalciuria and nephrocalcinosis may be a clue to an etiological diagnosis. These findings are distinctly uncommon in patients with Fanconi's syndrome, with one etiological exception: Wilson's disease. Patients with Wilson's disease and Fanconi's syndrome commonly have hypercalciuria and may have nephrolithiasis and nephrocalcinosis even before neurological abnormalities become apparent. The striking impairment in tubular reabsorption of uric acid demonstrated in the patient presented is particularly characteristic of the renal tubular dysfunction of Wilson's disease. Appropri-

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*[2] Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

*[3] R. Curtis Morris, Jr., M.D., Assistant Professor of Medicine.

TABLE 1.—*Classifications of Fanconi Syndrome*

I. IDIOPATHIC
 A. Sporadic
 B. Familial
II. AS PART OF A GENETIC DISEASE
 A. Cystinosis
 B. Wilson's Disease
 C. Tyrosinemia
 D. Lowe's Syndrome
 E. Hereditary Fructose Intolerance (with fructose)
III. MEDULLARY CYSTIC DISEASE
IV. ACQUIRED
 A. Abnormality of Protein Metabolism
 1. Nephrotic Syndrome
 2. Multiple Myeloma
 3. Sjögren's Syndrome
 4. Amyloidosis
 B. Drugs
 1. Outdated Tetracycline
 2. 6-Mercaptopurine
 3. Isophthalanilide
 C. Heavy Metals
 1. Mercury
 2. Uranium
 3. Cadmium
 D. Malignancy
V. EXPERIMENTAL (Animals)
 A. Maleic Acid
 B. Malonic Acid

ate diagnostic studies are in progress. A diagnosis of Wilson's disease would be critically important since the neurological complications of the disorder are preventable and in some instances reversible with penicillamine therapy.

In children, Fanconi's syndrome is most often recognized in association with cystinosis. By cystinosis I mean the genetically transmitted disorder in which "cystine storage" occurs in the cells of the renal tubule, the liver, spleen, as well as in the bone marrow and cornea. Cystine deposits in the cornea have been reported in adult patients without Fanconi's syndrome, but patients so affected appear to be quite uncommon. Lowe's syndrome, which includes Fanconi's syndrome, is a sex-linked, genetically transmitted disorder, characterized by extreme mental deficiency, cataracts, curious hyperextensibility of the joints and hyperstretchability of the skin.

Recently it has been demonstrated that the biochemical findings of Fanconi's syndrome can be experimentally induced in patients with hereditary fructose intolerance. Administration of fructose to these patients induces impaired tubular reabsorption of amino acids, glucose, phosphate and uric acid as well as lysozymuria, and a renal acidification defect with physiological characteristics usually considered diagnostic of renal tubular acidosis (RTA). In some patients with galactosemia and RTA, nephrolithiasis occurs and the experimental administration of galactose induces aminoaciduria. Our group has recently studied a child with medullary cystic disease of the kidney and Fanconi's syndrome.

Fanconi's syndrome occurs in several disorders of protein metabolism. These include the nephrotic syndrome, multiple myeloma and Sjögren's syndrome. The exact relationship of the protein abnormalities to tubular dysfunction in these syndromes is not clear. In the nephrotic syndrome and multiple myeloma, the proximal tubule has been postulated to reabsorb protein in a manner, in an amount or of a type which disrupts the structure and function of the tubule.

Findings of the Fanconi's syndrome have occurred in patients with a variety of tumors, including carcinomas of the ovaries and pancreas. Conceivably a humor released by the tumor may be causal.

Heavy metals have long been known to be a causal agent of aminoaciduria and glucosuria. Long-term exposure to cadmium may give rise to renal acidification defects as well. Drugs, especially outdated tetracycline, may cause Fanconi's syndrome in association with a renal acidification defect and renal "wasting" of potassium. The occurrence of Fanconi's syndrome has been described in a patient with the nephrotic syndrome after initiation of 6-mercaptopurine. Fanconi's syndrome is usually reversible when caused by drugs or heavy metals.

Some years ago the Harrisons in Baltimore induced the Fanconi syndrome in rats by the administration of maleic acid.[1] Dr. Robert Berliner and associates induced a renal acidification defect in dogs by administering maleic acid. These are interesting models in that maleic acid is a known inhibitor of sulfhydryl-containing enzymes. Earlier this year an abstract described the experimental induction of Fanconi's syndrome in rats with malonic acid, an inhibitor of succinic dehydrogenase.[2]

I would like to focus on two aspects of Fanconi's syndrome: the usually present renal acidification defect and the recently demonstrated lysozymuria. Patients with Fanconi's syndrome commonly have the triad of biochemical findings generally con-

sidered characteristic of RTA: alkaline or minimally acid urine, hyperchloremic acidosis and minimal or no azotemia. The renal acidification defect associated with the Fanconi syndrome, however, is separable from that of "primary" renal tubular acidosis (RTA) of adults. Primary renal tubular acidosis is used here to mean renal tubular acidosis which is not associated with a generally recognizable cause and not associated with the Fanconi syndrome.

In adults with primary RTA, the urine pH is inappropriately high during acidosis of even severe degree; bicarbonaturia is characteristic but quantitatively trivial. Because of their inappropriately high urinary pH, patients with primary RTA are unable to excrete titratable acid at normal rates; ammonium excretion is also curtailed. Accordingly, acid is excreted at a rate less than that at which nonvolatile acid is metabolically generated. Acidosis occurs and persists. The acidosis can be treated by titrating the endogenous, nonvolatile acid with exogenous alkali. Nonvolatile acid is produced at a rate of approximately a milliequivalent per kilogram per day, or 70 to 100 mEq. Hence, treatment with 70 to 100 mEq of alkali a day usually corrects the acidosis of patients with primary renal tubular acidosis.

In contrast to patients with primary RTA, those with the renal acidification defect of Fanconi's syndrome commonly decrease their urinary pH to normal minima and can excrete large amounts of acid, particularly if they become quite acidotic. With a lesser degree of acidosis, an inappropriately elevated urinary pH and urinary wasting of bicarbonate tend to occur. In many children with Fanconi's syndrome, sustained correction of acidosis is difficult because of the rate at which bicarbonate is "wasted" at reduced levels of plasma bicarbonate. In such patients alkali therapy may give rise to the combination of hyperchloremic acidosis and a urinary pH of 7.8 or greater. In adults with classic RTA, the urinary pH characteristically remains less than that of the blood — less than 7.3 — until hyperchloremic acidosis is corrected by alkali therapy.

In some adults with Fanconi's Syndrome, however, acidosis is readily corrected with alkali therapy, suggesting a renal acidification defect different from that of most children with Fanconi's syndrome.

I would like to consider in some detail the apparent mechanism of the acidification defect in

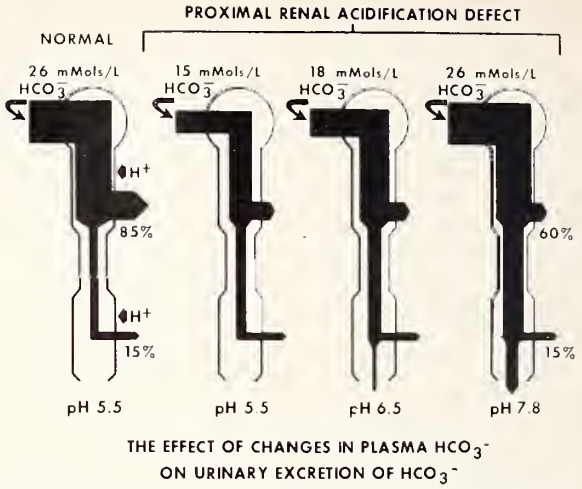


Chart 1.—Schematic diagram showing effect of changes in plasma bicarbonate concentration on urinary bicarbonate excretion and urinary pH in patients with a hydrogen ion secretory defect of the proximal nephron.

some patients with Fanconi's syndrome. Chart 1 is a diagrammatic representation of an acidification defect of the proximal tubule. This type appears to be characteristic of patients with Fanconi's syndrome as part of cystinosis, Lowe's syndrome, medullary cystic disease and hereditary fructose intolerance (during exposure to fructose). The diagram indicates the normal fractional distribution of bicarbonate reabsorption in the renal tubule. On the basis of micropuncture studies in rats and dogs, some 85 to 90 percent of bicarbonate is reabsorbed in the proximal nephron, 10 to 15 percent in the distal nephron. Presumably all bicarbonate "reabsorption" is accomplished by hydrogen ion secretion — H^+-Na^+ exchange. After bicarbonate is titrated to extinction in the distal nephron, continued H^+ secretion decreases urinary pH to 5.5 or lower. When the concentration of plasma bicarbonate is 26 mEq/L and proximal reabsorption of bicarbonate reduced to 60 percent of that which is filtered, the amount of bicarbonate unreabsorbed by the proximal nephron is greater than that which can be titrated by H^+ secretion in the distal nephron. As a result, bicarbonate excretion is brisk; urinary pH approaches 8. When the concentration of plasma bicarbonate decreases, the filtered load of bicarbonate and the amount of bicarbonate unreabsorbed by the proximal nephron also decreases. When the concentration of plasma bicarbonate decreases to 15 mEq per liter, the amount of bicarbonate escaping reabsorption by the proximal nephron is that amount normally titrated to

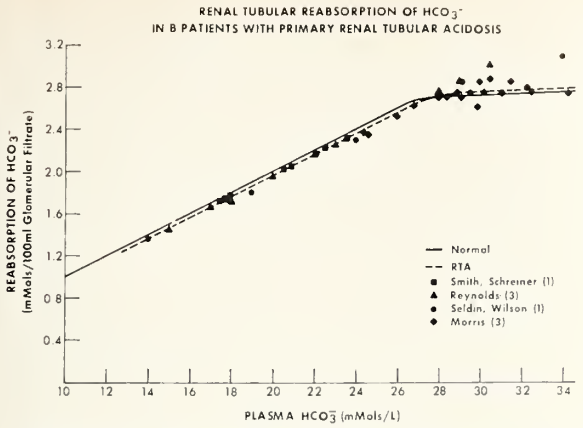


Chart 2.—Relationship between plasma concentration, renal tubular reabsorption and urinary excretion of bicarbonate in eight adults with renal tubular acidosis.

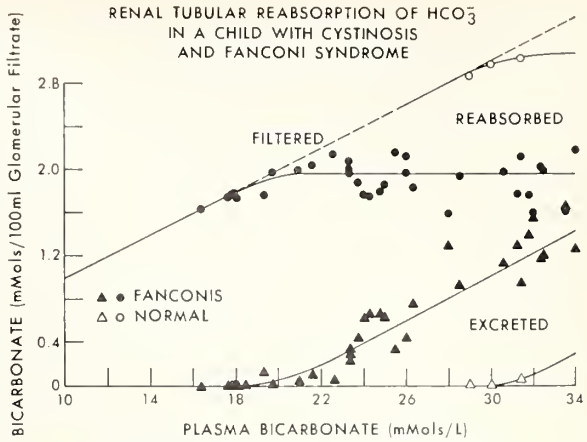


Chart 3.—Relationship between plasma concentration, renal tubular reabsorption and urinary excretion of bicarbonate in a child with cystinosis and Fanconi's syndrome.

extinction by the acidification process of the distal nephron. Excretion of bicarbonate stops and urinary pH decreases to 5.

We might look now at some data on the renal handling of bicarbonate in subjects with normal and abnormal mechanisms of renal acidification. Chart 2 shows the relationship between the concentration of plasma bicarbonate and the tubular reabsorption of bicarbonate in both normal subjects and in adults with primary RTA. Normally urinary excretion of bicarbonate is negligible until the concentration of plasma bicarbonate is increased to approximately 26 mEq per liter. That is, bicarbonate reabsorption is almost complete until the concentration of plasma bicarbonate exceeds 26 mEq per liter both in normal persons and in patients with classic RTA. Further increases in the amount of bicarbonate filtered result in no further increase in bicarbonate reabsorption. Accordingly, in adults with primary RTA the maximal capacity to reabsorb bicarbonate — so-called Tm HCO_3^- — is the same as that in normal subjects. Chart 3 depicts the relationship between the tubular reabsorption of bicarbonate and the concentration of plasma bicarbonate in a child with cystinosis and Fanconi's syndrome. The "bicarbonate titration curve" is fitted to points derived from four separate studies. At a concentration of plasma bicarbonate of 20 mEq per liter the tubular reabsorption of bicarbonate has reached a maximum. In contrast, a normal child wastes insignificant amounts of bicarbonate until the plasma bicarbonate is increased to approximately 26 to 28 mEq per liter. Tm HCO_3^- is therefore reduced by 20 to 30 percent in the patients with Fanconi's syndrome. A reduction in Tm HCO_3^- of greater than 25 percent presumably could not result solely from even obliteration of the acidification process of the distal nephron. In the child with Fanconi's syndrome, administration of bicarbonate would result in bicarbonate wasting when the concentration of plasma bicarbonate approached 19 to 20 mEq per liter.

Chart 4 depicts bicarbonate titration curves from studies of five patients with Fanconi's syndrome. It is apparent that the magnitude of the H^+ secretory defect in Fanconi's syndrome varies considerably from patient to patient. It is also apparent that the patient presented today had no demonstrable defect in reabsorption of bicarbonate. After ammonium chloride loading the urinary pH decreased to normal minima — less than 5 — and the urinary excretion of titratable acid

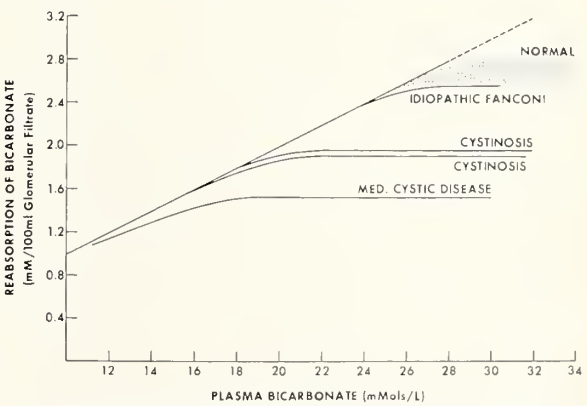


Chart 4.—Relationship between plasma concentration, renal tubular reabsorption and urinary excretion of bicarbonate in children with Fanconi's syndrome of several clinical types.

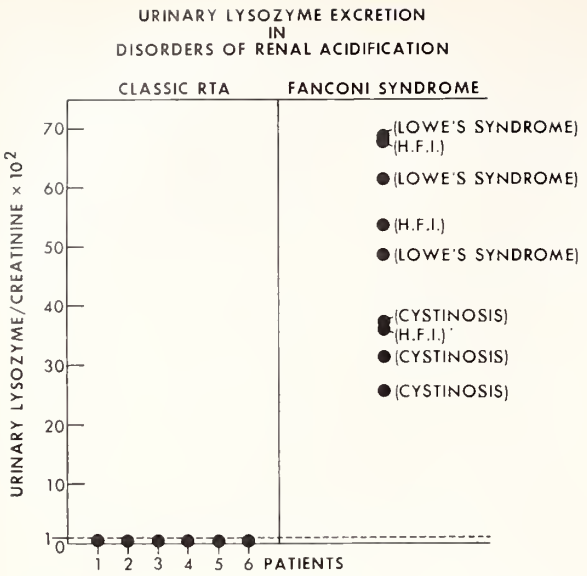


Chart 5.—Urinary lysozyme excretion in patients with classic renal tubular acidosis (RTA) and in patients with clinical and experimental (Hereditary Fructose Intolerance—HFI) Fanconi's syndrome.

and ammonium increased to normal maxima. The patients with cystinosis and Lowe's syndrome have striking impairments in tubular reabsorption of bicarbonate, and the patient with medullary cystic disease has an even greater impairment. In the patients with cystinosis, bicarbonate excretion disappeared at concentrations of plasma bicarbonate of 16 to 18 mEq per liter; urinary pH decreased to less than 5.5. In the patient with medullary cystic disease, large amounts of bicarbonate were excreted even when the concentration of plasma bicarbonate decreased to 10 mEq per liter; urinary pH decreased only to 7.0. Unlike the acidification defect of the proximal nephron formulated earlier and apparently operative in the two patients with cystinosis, the acidification defect of the patient with medullary cystic disease probably involves the distal nephron as well as the proximal nephron. A structural abnormality of the medullary portion of the distal nephron has previously been invoked to explain the severe vasopressin-resistant concentrating defect of these patients.

How might we further separate the renal tubular dysfunction of primary RTA from that of Fanconi's syndrome? Prockop and Davidson[3] suggested that the urinary excretion of lysozyme, an enzyme first described by Sir Alexander Fleming, might reflect a relatively specific indication of tubular damage. Lysozyme activity can be localized to renal lysosomes. These are cytoplasmic organelles bounded by a single membrane, the integrity of which is vulnerable to a variety of metabolic insults. It has been shown in experimental animals that several heavy metals will produce lysozymuria as well as glucosuria and aminoaciduria. We were interested in the notion that lysozyme might leak through lysosomal membranes labilized by metabolic derangement of the cells of the proximal nephron. In patients with Fanconi's syndrome the usual accompaniment of a systemic metabolic disease and the diversity of proximal tubular dysfunction suggest the possibility that the mechanism of the tubular dysfunction may involve a disturbance of renal metabolism at some point removed from the several affected transport processes. On the other hand patients with primary RTA by definition do not have the diverse dysfunction of the proximal tubule characteristic of Fanconi's syndrome. Moreover, the reported patients with primary RTA, whether sporadic or familial in occurrence, have had no demonstrable systemic metabolic diseases.

We first looked at lysozyme excretion in patients with hereditary fructose intolerance. Lysozymuria became quite striking in these patients during the administration of fructose and disappeared after fructose was stopped. Chart 5 shows the absence of lysozymuria in six patients with primary RTA and the occurrence of lysozymuria in patients with a variety of disorders characterized by the occurrence of the Fanconi syndrome. The patient presented today had pronounced lysozymuria.

I should point out that lysozyme is a very small protein with a molecular weight of less than 20,000. It probably is filtered by the glomerulus and reabsorbed by the proximal tubule. Lysozymuria in patients with Fanconi's syndrome may then be just another characteristic of impaired proximal tubular function.

DR. SMITH: We have time for comments and questions concerning Fanconi's syndrome in general and the two aspects of it which Dr. Morris has particularly emphasized, namely the acidification abnormalities and the lysozymuria.

DR. FUDENBERG*[4]: I gather that urinary lysozyme is increased in bacterial infection of the urinary tract, during the rejection crisis of a transplanted

*[4]H. Hugh Fudenberg, M.D., Professor of Medicine.

kidney, and is also greatly increased in patients with certain forms of leukemia, as shown by Osserman and others.[4] Here lysozymuria might result from an infiltration of the kidney by leukocytes. Has anyone looked at the blood of patients with Lowe's syndrome or similar disorders with lysozymuria to see if mononuclear cells are abnormal or contain inclusions in increased numbers?

DR. MORRIS: Three of the six patients with RTA depicted in Chart 5 had clinical pyelonephritis, yet none had lysozymuria comparable to that found in patients with the Fanconi syndrome. The serum lysozyme levels were either normal or slightly increased in both groups of patients. I am aware of the work of Osserman and Lawlor in which high concentrations of lysozyme were reported in the blood and urine of ten patients with monocytic leukemia.[4] Of interest is the fact that five of those patients had renal wasting of potassium.

DR. FUDENBERG: Are there inclusions in circulating leukocytes in patients with cystinosis?

DR. MORRIS: Yes, there are inclusions of cystine crystals in circulating granulocytes in patients with cystinosis.

DR. EDELMAN*[5]: Has anyone studied the ability of patients with proximal renal tubular acidosis to produce an acid gastric juice, or to remove bicarbonate in sweat? That is, do they have an intact bicarbonate transport system in the sweat gland and an intact hydrogen transport system in the gastric mucosa?

DR. MORRIS: In a number of patients with RTA, the ability of the stomach to make acid has been investigated. The ones who were studied could. I have no information on sweat.

DR. SMITH: That concludes the session for today.

REFERENCES

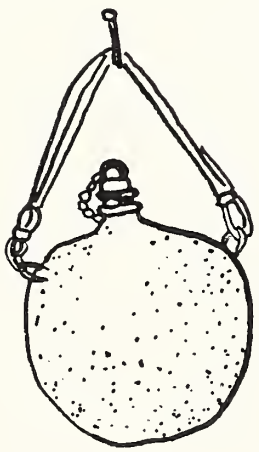
1. Harrison, H. E., and Harrison, H. C.: Experimental production of renal glycosuria, phosphaturia and aminoaciduria by injection of maleic acid, Science, 120:606, 1954.

2. Ludwig, G. D., Chaykin, L. B., and Scott, R. McN.: Fanconi syndrome in rats inhibiting succinic dehydrogenase with malonate, Intl. Congress Nephrology III. II. Free Communications, pp. 234, Sept. 1966.

3. Prockop, D. J., and Davidson, W. D.: A study of urinary and serum lysozyme in patients with renal disease, New Eng. J. Med., 270:269, 1964.

4. Osserman, E. F., and Lawlor, D. P.: Serum and urinary lysozyme (muramidase) in monocytic and monomyelocytic leukemia, J. Exper. Med., 124:921, 1966.

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EDITORIAL

A Century of Restless Progress

This issue of CALIFORNIA MEDICINE is largely devoted to commemorating the Centennial of the Sacramento Society for Medical Improvement and its distinguished contributions to the promotion "of the art and science of medicine and the advancement of the public health" in the course of a hundred years. During this time California has grown to become the most populous state in the Union. Though bawdiness and lawlessness may have somewhat diminished, restlessness, innovation and enterprise are still everywhere in the air. Much persists that smacks of the frontier. In many ways the eyes of the nation are just as much on California today as they were a hundred years ago.

The articles to be found elsewhere in this issue reflect the past, present and future, not only of the Sacramento Society for Medical Improvement, but of California medicine as a whole. The Sacramento physicians who wrote these articles are clearly the energetic descendants of their forebears they describe, and also proud examples of the drive and sophistication which distinguishes the medical profession throughout California. The editors thank these special contributors and particularly acknowledge the tireless effort of Dr. Edmund E. Simpson of Sacramento for his work in preparing this "Sacramento issue" of CALIFORNIA MEDICINE. We join with all California physicians to wish the Sacramento Society for Medical Improvement another century of restless progress.

Sacramento Society for Medical Improvement: The Centennial

ON 17 MARCH 1868, 12 Sacramento physicians met at 46 J Street to form the Sacramento Society for Medical Improvement. The model for this name was said to have been the Boston Society for Medical Improvement. There had been earlier societies in Sacramento. The first medical society in California, the Medico-Chirurgical Association of Sacramento, was founded in 1850. That organization disbanded after four or five years. The Sacramento Medical Society was formed in 1855 and lasted until 1863. The Sacramento County Pathological Society, which began life in 1858, died in infancy. The present Society has been in continuous existence since its inception.

To be one hundred years old is good reason to examine whence we came and whither tending. The Sacramento Society has a rich background. The CALIFORNIA STATE JOURNAL OF MEDICINE first appeared in July 1856. It was printed at the plant of the Sacramento Union. The first railroad hospital was built here. The Sacramento Board of Health, the second in the United States, was formed three months after the first was founded in Boston. Through the influence of Sacramento physicians came the first State Board of Health. The *Sacramento Medical Times* was started in 1887 and at that time was said to be the best of the medical journals in California in content, style and format.

Twelve Sacramento physicians have been president of the California Medical Association, and one of them, Dr. Thomas Logan, was president of the American Medical Association. He was the first California physican to be so honored. Dr. Logan was perhaps the greatest influence in the history of Sacramento medicine. One of the astonishing things about the early leaders of medicine in Sacramento was the incredible number of organizations to which they actively contributed and the remarkable number of scientific articles they were able to write. Horse and buggy days, indeed!

But Sacramento has its modern counterparts, which the future will more properly place in perspective. One of the exciting developments in this region is the new medical school on the Davis campus of the University of California, guided by an enthusiastic dean and staff. The rapid growth of medical facilities in Sacramento has come about without the loss of what is perhaps the most significant feature of our Society: The members look upon one another as friends and colleagues rather than as competitors. A fine *esprit de corps* prevails, which will enhance the numerous conferences and symposiums planned in celebration of the anniversary.

In recognition of the centennial celebration Dr. Dwight L. Wilbur, former editor, and Dr. Malcolm S. M. Watts, present editor, and the Editorial Board of CALIFORNIA MEDICINE have graciously permitted members of the Sacramento Society for Medical Improvement to contribute the scientific articles for this, the March issue. The Society and the authors are grateful for the opportunity to publish these papers which represent some of the present medical thought in the Sacramento Valley.

EDMUND E. SIMPSON, M.D.
Sacramento

Chemical Examination

IN RESPONSE TO the constantly growing demand for both old and new laboratory tests, physicians and industry have designed instruments for automated or semi-automated performance of laboratory tests which promise to provide larger numbers of tests at lower costs. Some physicians have hailed this development and advocated "complete laboratory examination" to accompany the complete physical. Others have warned against abrogating clinical judgment in favor of multichannel test packages and have pleaded for more critical care in ordering tests. Whatever the merits of the opposing arguments, the geometric progression of tests ordered continues with a doubling time of four to five years as it has for the past 20 years. The trend now has all the earmarks of the "inevitability of progress." Perhaps the time has come to examine the practical uses of the proliferation of automated laboratory services rather than argue their merits.

The paper by Glassy and Blumenfeld elsewhere in this issue appears as a first and welcome step in that direction. As they imply, the outstanding advantage of automation is the ease of repetitive performance. In itself, this may lead merely to making the same mistake over and over again. In technical terms, precision does not imply accuracy. More bluntly, the result is not necessarily right, even if it is endlessly reproducible by the tireless machine.

In another context, the ease of repetitive examination offers the opportunity of defining not only normal values for a population but also the much narrower range within which individuals maintain their biochemical and hematologic parameters. Can we then hope to predict disease when an individual moves beyond his own range of normal, perhaps even if he remains within the boundaries of the normal values for the whole population? An example can be given. With a certain method the normal range of serum uric acid values for males between 40 and 60 years of age may be taken as 4 to 8 mg per 100 ml. Let it be assumed that there are two individuals whose uric acid levels had strayed between 4 and 4.5 mg per 100 ml and between 7.5 and 8.0 mg per 100 ml, respectively, for many years. Is the new appearance of a uric acid value of 6.5 mg per 100 ml as ominous in the first individual as 10.5 mg per 100 ml in the second? It appears imperative that these questions be answered before large scale repetitive laboratory examinations are begun in the name of preventive medicine. Even if it turns out that variations by the individual from his own norm improves the predictive value of laboratory examinations, repetitive tests may still not be useful unless the prediction can be translated into preventive action. Prognosis, however, has almost always preceded development of therapy. We may hope that better un-

derstanding of the natural history of diseases, provided in part by such studies as now undertaken by Glassy and Blumenfeld, will eventually lead to improvement of our therapeutic as well as our prognostic armamentarium.

A Commission on Medical Economics

DURING A CENTURY of increasing evidence of man's terrifying destructive capabilities, the medical profession has steadfastly labored for the improvement of mankind.

In the understanding of disease processes, in the cure and amelioration of disease and in the search for hitherto unidentified disease, the progress of the past century surpasses all of the advances of preceding years.

While it would seem quite proper at a centennial celebration to list in great detail the glories of the past, what is to be gained thereby? The benefits of previous discoveries are already here. Better, at this time of celebration, that we take upon ourselves the responsibility of seeking out those areas wherein our predecessors, great as they were, did not fulfill their own aspirations.

Specifically we can concern ourselves with the financing and distribution of medical care. A mature and responsible medical society should recognize the existence of the gap between available medical knowledge and the delivering of it to those who need it. Unfortunately, the medical genius of the past has been so engrossed in the scientific aspect of disease that it had little time to concern itself with the mundane problems of distribution of medical care. The simple market transaction involved in getting medical care to the patient was somehow or other not a primary medical concern.

It is now abundantly clear that the public will tolerate nothing short of adequate medical care available to the entire body politic. The only problem at issue is whether this care is to be provided in conformity with our current economic structure or through a system of taxation. The medical profession can no longer struggle from expediency to expediency while others seek out and identify deficiencies in the distribution of medical care. The clock is running out. Each year brings an additional program of tax-supported medicine. Neither of the major political parties can possibly turn the clock back. If there is to be a desirable solution to the problem of financing and distributing medical care, a great part of the solution must come from the medical profession itself. Either we assume the leadership in sponsoring and developing programs within the economic reach of every person or we forfeit to government.

Organized medicine alone is obviously in no position to solve the social and economic problems associated with the marketing of medical care. The multiplicity of disciplines providing care and the varied mechanisms in vogue for financing it make a unilateral approach inadequate. A durable solution can be expected only if all the providers, underwriters and recipients of service are represented and involved in the planning process. It is necessary that the medical profession, representatives of the insurance industry, hospital associations, allied disciplines, government, educational institutions and consumer groups join in a combined endeavor.

Today our future depends on strength of leadership. Financial means are available, medical knowledge is abundant. Only the techniques of the market transaction are lacking. Does it not seem prudent, therefore, to form a commission on the economics and distribution of medical care and to charge that commission with the responsibility of studying the problems entailed in bringing all the involved parties into comfortable partnership. It is expected that a joint effort, led by the medical profession would challenge all the participants: Government representatives, insurance executives, consumer representatives, physicians and allied health personnel — all would be placed in a position of responsibility for the outcome.

The popularity of federalized medicine is based almost exclusively on the economic problems associated with illness. It is extremely doubtful that, given reasonable alternatives, the public would trade private care for government care. It is quite obvious today that our generation faces the challenge of finding the alternatives. A commission on medical economics seems a most logical beginning.

A. E. BERMAN, M.D.
Sacramento

California Medical Association

Council Highlights

Highlights of the Actions of the California Medical Association 540th Council Meeting, 13 January 1968, San Francisco

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA Headquarters office or your component society.

Professional Liability Legislation will be developed by the CMA Committee on Legislation at the request of the Council. To be introduced during this session of the California Legislature, the proposals will be based upon the eight points of testimony presented to the Senate Interim Committee by CMA Legal Counsel Howard Hassard last December and approved at the December Council meeting.

A Definition of Residential Maintenance Care developed by the Commission on Hospital Affairs was approved. The new definition:

> *Residential (custodial-domiciliary) maintenance care* is defined as care which is required to assist a person in carrying out the usual activities of daily living. These activities are:
>
> Moving about in bed
> Sitting up
> Getting in and out of bed
> Locomotion by any means suitable to the person's condition
> Eating
> Dressing
> Bathing
> Toilet activities
>
> Also included shall be such functions as dispensing oral and parenteral medication as might normally be ordered by the physician and administered at home under the supervision of the family or home health agency.
>
> Persons who need assistance purely in performance of the above activities are deemed to require residential or maintenance care. Persons needing professional care beyond the simple services enumerated above are deemed to require other levels of patient care.

JOHN G. MORRISON, M.D. President
MALCOLM C. TODD, M.D. President-Elect
WILLIAM F. QUINN, M.D. Speaker
JOSEPH F. BOYLE, M.D. Vice-Speaker
ALBERT G. MILLER, M.D. Chairman of the Council
HAROLD KAY, M.D. Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D. Secretary
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1127 11th St., Sacramento 95814 • 916 444-7496

A CMERF Program for Undergraduate Scholarships to be administered through the National Merit Scholarship Corporation was approved. During the first year, six or seven four-year grants will be made to California high school seniors who indicate they intend to enter the health care field. County medical societies will be asked to help screen qualified candidates, and final selection will be made by CMERF.

A Statement Supporting Clinical Laboratory Proficiency Testing by specialty societies as a requirement for membership was approved. It was also suggested that the Advisory Committee on Clinical Laboratory Performance Evaluation to the Division of Laboratories, California State Department of Public Health, continue its activities in an advisory capacity.

Albert G. Clark, M.D., Was Elected New Eighth District Councilor, to fill the vacancy in the councilor office previously held by Malcolm S. M. Watts, M.D., now editor of CALIFORNIA MEDICINE.

Four Physician Members of the Blue Shield Board of Trustees whose terms expire this year were approved to be placed in nomination before the CMA House of Delegates in March for election to new terms of office. The four are: Richard F. Altman, M.D., Newport Beach; Burt L. Davis, M.D., Palo Alto; Donald R. Fitch, M.D., Glendale, and Bert Halter, M.D., San Francisco.

Named to the Audio-Digest Board of Directors for 1968-69 were Doctors Gorden B. Beckner, Henry V. Eastman, William D. Evans, Elmer F. Gooel, George C. Griffith, Merlin A. Hendrickson, Donald D. Lum, Robert L. Marsh, John W. Pender, Keith P. Russel, Edward B. Shaw, and Messrs. K. L. Hamman and Claron L. Oakley.

Appointed to the Committee on Emergency Medical Care were Walter Ellerback, M.D., Los Angeles, as an additional member, and A. J. Franzi, M.D., San Francisco, as consultant.

Recent Medi-Cal Developments included a report on the suit filed by the California State Employees Association against Blue Shield and others saying that a state bureau should be fiscal agent for the Medi-Cal program. To date, two demurrers filed by the defendants have been accepted by the court; a second amended complaint has been filed by the CSEA, to which another demurrer is expected to be filed by the defendants.

A Survey on the Licensing of X-Ray Technicians will be carried out by the Committee on Legislation at the request of the Council.

Each County Must Establish a Committee on Emergency Medical Services by July 1, 1968, Carl Anderson, M.D., chairman of the CMA Committee on Emergency Medical Care, told the Council. The committee is required by A.B. 2276 to review, at least annually, the ambulance and emergency medical care services available within the county, as well as first aid practices in the county.

A Report on the Conference on Health Manpower Distribution in Rural California, of which L. J. Snyder, M.D., was chairman, and which included these recommendations, was approved:

- CMA should conduct periodic studies of the distribution of rural health manpower.
- CMA should recommend to the Health Manpower Council that distribution of health manpower should be an early concern of that organization.
- Medical schools should be urged to consider the adequate inclusion of community manpower in their curriculum.
- CMA should work more closely with student medical groups.

In Memoriam

AKAMATSU, GEORGE TARO, Sacramento. Died 12 January 1968, aged 68. Graduate of Emory University School of Medicine, Atlanta, Georgia, 1936. Licensed in California in 1938. Doctor Akamatsu was a member of the Sacramento County Medical Society.

✣

BECKA, STANISLAUS JOHN, Los Angeles. Died 1 February 1968 in Los Angeles of bronchopneumonia due to ruptured aneurysm of abdominal aorta, aged 76. Graduate of St. Louis University School of Medicine, 1915. Licensed in California in 1916. Doctor Becka was a member of the Los Angeles County Medical Association.

✣

BROOKS, CHARLES S., El Centro. Died 13 January 1968 in El Centro of heart disease, aged 80. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1911. Licensed in California in 1915. Doctor Brooks was a member of the Imperial County Medical Society.

✣

CLIFF, LLOYD WILLIAM, South Pasadena. Died 12 November 1967 in San Gabriel of postoperative shock, aged 57. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1937. Licensed in California in 1937. M.D. degree from the California College of Medicine, 1962. Doctor Cliff was a member of the Forty First Medical Society.

✣

CLOCK, CHARLES JOSEPH, Newport Beach. Died 14 January 1968 in Costa Mesa, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1933. Licensed in California in 1933. Doctor Clock was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

DAVIS, HARRY H., El Segundo. Died 11 January 1968 in El Segundo, aged 77. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1916. Licensed in California in 1917. Doctor Davis was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

DOOLEY, ROBERT F., Oakland. Died 17 January 1968 in Oakland of arteriosclerosis of coronary arteries, aged 49. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1943. Licensed in California in 1944. Doctor Dooley was a member of the Alameda-Contra Costa Medical Association.

FAVERMAN, ANITA E., San Francisco. Died 25 October 1967 in San Francisco of anaplastic carcinoma, aged 65. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1925. Licensed in California in 1925. Doctor Faverman was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

FOREE, LYNN, Oakland. Died 24 January 1968 in Oakland of arteriosclerotic heart disease, aged 64. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1929. Licensed in California in 1929. Doctor Foree was a member of the Alameda-Contra Costa Medical Association.

✣

HOPKINS, IRA JAY, Mountain View. Died 24 December 1967 in Mountain View of cerebral vascular accident, aged 75. Graduate of George Washington University School of Medicine, Washington, D.C., 1921. Licensed in California in 1930. Doctor Hopkins was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

HUGHES, ALTON G., Costa Mesa. Died 31 January 1968 in Costa Mesa of coronary artery disease, aged 62. Graduate of Rush Medical College, Chicago, Illinois, 1937. Licensed in California in 1937. Doctor Hughes was a member of the Orange County Medical Association.

✣

JACKSON, DONALD DEAVILA, Palo Alto. Died 29 January 1968 in Foster City, aged 48. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1943. Licensed in California in 1944. Doctor Jackson was an associate member of the Santa Clara County Medical Society.

✣

KARTOON, LOUIS B., Los Angeles. Died 10 January 1968 in Los Angeles, aged 65. Graduate of Rush Medical College, Chicago, Illinois, 1925. Licensed in California in 1945. Doctor Kartoon was a member of the Los Angeles County Medical Association.

✣

KERSTEN, HUGO M., Los Angeles. Died 28 January 1968 in Los Angeles of myocardial infarction, aged 73. Graduate of the College of Physicians and Surgeons, Los Angeles, 1921. Licensed in California in 1922. Doctor Kersten was a member of the Los Angeles County Medical Association.

KESER, MARGUERITE DEININGER, Richmond. Died 23 January 1968 in San Pablo of multiple myeloma, aged 91. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1902. Licensed in California in 1902. Doctor Keser was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

KLABUNDE, E. HORACE, San Francisco. Died 26 January 1968 in San Francisco, aged 58. Graduate of Marquette University School of Medicine, Milwaukee, Wisconsin, 1933. Licensed in California in 1934. Doctor Klabunde was a member of the San Francisco Medical Society.

⁂

KLING, DAVID HIRSCH, Los Angeles. Died 17 January 1968 in Los Angeles of multiple myeloma, aged 76. Graduate of Medizinische Fakultät der Universität, Wein, Austria, 1916. Licensed in California in 1925. Doctor Kling was a member of the Los Angeles County Medical Association.

⁂

LISSNER, HENRY HYMAN, Los Angeles. Died 28 January 1968 in Los Angeles of arteriosclerotic heart disease, aged 92. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1903. Licensed in California in 1904. Doctor Lissner was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

⁂

MCHUGH, PATRICK HENRY, Stockton. Died 29 November 1967 in Stockton of heart disease, aged 64. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1931. Licensed in California in 1931. Doctor McHugh was a member of the San Joaquin County Medical Society.

⁂

MILLIGAN, EDWIN C., Fullerton. Died 5 February 1968 in Fullerton of coronary artery disease, aged 46. Graduate of University of Southern California School of Medicine, Los Angeles, 1955. Licensed in California in 1956. Doctor Milligan was a member of the Orange County Medical Association.

⁂

PLETH, VALDEMAR, Santa Rosa. Died 23 October 1967 of pneumonia and heart disease, aged 98. Graduate of University of Illinois College of Medicine, Chicago, 1899. Licensed in California in 1899. Doctor Pleth was a member of the Sonoma County Medical Society.

⁂

PROESCHER, FREDERICK, San Jose. Died 29 November 1967, aged 92. Graduate of Universität Basel, Medizinische Fakultät, Switzerland, 1899. Licensed in California in 1923. Doctor Proescher was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

RUMPH, PAUL E., Orange. Died 25 January 1968 in Orange of malignant disease, aged 64. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1930. Licensed in California in 1930. Doctor Rumph was a member of the Orange County Medical Association.

⁂

SYLVESTER, JOHN H., Los Angeles. Died 18 December 1967 in Newport Beach, aged 53. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. M.D. degree from California College of Medicine, 1962. Doctor Sylvester was a member of the Los Angeles County Medical Association.

⁂

TANDOWSKY, RALPH MYRON, Los Angeles. Died 18 January 1968 in Los Angeles of congestive heart failure, aged 67. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1922. Licensed in California in 1922. Doctor Tandowsky was a member of the Los Angeles County Medical Association.

⁂

THOMPSON, RAYMOND CHARLES, Whittier. Died 11 January 1968 in Whittier of heart disease, aged 80. Graduate of Rush Medical College, Chicago, Illinois, 1920. Licensed in California in 1921. Doctor Thompson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

THOMPSON, RODERICK A. I., Orinda. Died 27 January 1968 at Sea Ranch, Stewarts Point (Sonoma County) of coronary artery thrombosis, aged 59. Graduate of the University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Doctor Thompson was a member of the Alameda-Contra Costa Medical Association.

REGIONAL CENTENNIAL SYMPOSIUM FOR SACRAMENTO VALLEY COUNTIES

El Dorado Hotel
Sacramento
Saturday-Sunday
May 4-5, 1968

SACRAMENTO VALLEY COUNTIES

Presented cooperatively by Sacramento Society for Medical Improvement, University of California, Davis, School of Medicine and California Medical Association Committee on Continuing Medical Education. A 14-hour course.

HOST: Sacramento Society for Medical Improvement
Program Co-Chairmen: Richard C. Ripple, M.D. and Robert J. Bolt, M.D.

NO FEE: For additional information contact Continuing Medical Education office, California Medical Association, 693 Sutter Street, San Francisco 94102. All California Medical Association members and their families are cordially invited to attend.

GUEST SPEAKERS: William Bennett Bean, M.D., Iowa City, Iowa; B. Marden Black, M.D., Rochester, Minn.; Edwin H. Ellison, M.D., Milwaukee, Wisc.; Edward Gaensler, M.D., Boston, Mass.; Andrew A. Gage, M.D., Buffalo, N. Y.; C. Walton Lillehei, M.D., New York City; Earle M. Marsh, M.D., San Francisco; Samuel Perzik, M.D., Los Angeles; H. Marvin Pollard, M.D., Ann Arbor, Mich.; Henry K. Ransom, M.D., Ann Arbor, Mich.; John Raymond Smythies, M.D., Edinburgh, Scotland; H. J. C. Swan, M.D., Los Angeles and Willet F. Whitmore, Jr., M.D., New York City.

PROGRAM THEMES

THE UBIQUITOUS LUMP . . . THE EVALUATION OF YOUR CARDIAC PATIENT

SATURDAY, MAY 4

MORNING SESSION

THE UBIQUITOUS LUMP

Chairman: Robert J. Bolt, M.D.

8:45—Welcome—Pierce A. Rooney, Jr., M.D., President, Sacramento Society for Medical Improvement.

8:55—The Present Status of the Medical School—C. John Tupper, M.D., Dean, University of California, Davis, School of Medicine.

9:15—The Lump in the Breast—Henry K. Ransom, M.D.

9:45—The Asymptomatic Mass in the Neck—Samuel Perzik, M.D.

10:45—Nodular Goiter—B. Marden Black, M.D.

11:30—Panel Discussion
Moderator: Hamilton S. Davis, M.D.
B. Marden Black, M.D., Samuel Perzik, M.D. and Henry K. Ransom, M.D.

12:15—Luncheon
Presiding: Captane P. Thomson, M.D.
Biochemical Research in Schizophrenia – John Raymond Smythies, M.D.

AFTERNOON SESSION

THE UBIQUITOUS LUMP

Chairman: Earl F. Wolfman, Jr., M.D.

1:30—The Scrotal Enlargement—Willet F. Whitmore, Jr., M.D.

2:15—The Pelvic Adnexal Mass—Earle M. Marsh, M.D.

3:15—Solid Endocrine Tumors of the Pancreas—Edwin H. Ellison, M.D.

4:00—Abdominal Masses—H. Marvin Pollard, M.D.

4:45—Panel Discussion
Moderator: Robert S. Stempfel, Jr., M.D.
Edwin H. Ellison, M.D., Earle M. Marsh, M.D., H. Marvin Pollard, M.D. and Willet F. Whitmore, Jr., M.D.

The Saturday program made possible by a grant from Merck Sharp & Dohme.

SUNDAY, MAY 5

MORNING SESSION

THE EVALUATION OF YOUR CARDIAC PATIENT

Chairman: Edward J. Hurley, M.D.

9:00—The Complete Cardiac Evaluation: When and How—H. J. C. Swan, M.D.

9:40—Pacemakers: Their Uses and Complications—Andrew A. Gage, M.D.

10:40—Pulmonary Function Studies: Their Importance in Patients with Heart Disease—Edward Gaensler, M.D.

11:20—Surgical Considerations in Chronic Heart Disease —C. Walton Lillehei, M.D.

12:00—Panel Discussion
Moderator: Edward J. Hurley, M.D.
Edward Gaensler, M.D., Andrew A. Gage, M.D., C. Walton Lillehei, M.D. and H. J. C. Swan, M.D.

12:30—Luncheon—Annual Medical Lecture
Sponsored by the Honorable Board of Supervisors of Sacramento County.
Introduction: A. John Quinn, M.D., Chief of Staff, Sacramento County Hospital.
William Bennett Bean, M.D.

The Sunday program made possible by a grant from Wyeth Laboratories.

WOMAN'S AUXILIARY

to the California Medical Association

AMA-ERF

IF YOU CAN answer the following five questions, read no farther—you are 100 per cent informed on AMA-ERF!

1. What do the letters "AMA-ERF" denote?
2. Name two of the three programs of AMA-ERF supported by the Woman's Auxiliary to the American Medical Association.
3. Does medicine in California benefit from AMA-ERF?
4. How much did the California Medical Association and the Woman's Auxiliary to the California Medical Association raise and contribute to AMA-ERF in 1967?
5. Out of every dollar donated, what percentage is used for administration of AMA-ERF?

If you passed, congratulations! If you have unanswered questions, here are the answers:

• The American Medical Association Education and Research Foundation serves the dual purposes of providing financial assistance to medical education and scientific research.

• The Woman's Auxiliary supports three programs of AMA-ERF: Funds for Medical Schools, Loan Guarantee Program and the Institute for Biomedical Research. For quality medical education, medical schools need financial aid not only from the government but from private sources such as the medical profession. Private funds will continue to encourage medical schools to retain their independence. The Loan Guarantee Program assists in financing a medical education without a subsidy of any kind. The government will assist medical students but there is nothing available for interns and residents. For every dollar donated, banks participating in this program will lend $12.50 at 6.5 per cent interest. Where else does your dollar have such power?

• The Institute for Biomedical Research creates a place free from arbitrary restrictions where scientists can combine their skills and creativity in basic research so vital to health sciences.

• This past year, California medical schools benefited from the AMA-ERF as follows:

Loma Linda	$38,194.40
Stanford	33,436.22
California, San Francisco	3,870.38
Southern California	35,033.19
California, Los Angeles	3,873.37
California College of Medicine	87,818.88
California, San Diego	3.00
California, Davis	16,535.00

• A total of 3,835 California medical students, interns, and residents have borrowed a total principal amount of $4,593,273 over the past four years.

• In 1967, the California Medical Association presented a check to AMA-ERF in the amount of $108,227.50. The Woman's Auxiliary to the California Medical Association won a National award for their contribution of $48,233.57. Every cent of every dollar contributed is utilized because the American Medical Association underwrites *all* expenses of the Foundation. ALL contributions are income tax deductible. The Woman's Auxiliary to the California Medical Association works diligently on this top priority project. Will you help by giving to your member wife a check for the AMA-ERF—Auxiliary Fund?

MRS. WARD L. HART, AMA-ERF *Chairman*

PUBLIC HEALTH REPORT

Hamlet C. Pulley, M.D.
Acting Director, State Department of Public Health

We Have the Means to Eradicate Measles

WITH THE DEVELOPMENT of measles vaccine, we have the means to eradicate measles to the degree we have eradicated paralytic poliomyelitis. The year 1967 was "Measles Eradication Year" and California participated in this effort. Considerable progress has been made but there is much to do before measles can be wiped out in California. This goal cannot be reached without the support of local medical societies.

Several factors make measles immunization campaigns relatively simple. Only one immunization is necessary. Live attenuated measles virus vaccines are among the safest immunizing agents available and they appear to confer lasting protection against naturally occurring measles. It is not necessary to immunize the entire population, as in the case of poliomyelitis, since 90 percent of the population over 15 has had measles. Programs need be directed only at persons between the age of 12 months and 15 years with no immunization or clinical history of measles. In California about 80 percent of reported cases in recent years (1963-1966) have occurred in children under the age of ten, and 98 percent in persons under 20.

Perhaps the only real disadvantage in measles immunization is the fact that parenteral administration of vaccine is more complicated than oral administration. The use of the hypospray injector mitigates this difficulty.

From October 1965 through June 1967 a total of 388,790 measles immunizations were given in California by immunization projects affiliated with the Immunization Assistance Program of the State Department of Public Health. They were administered in health clinics, at special measles clinics of local health departments and in mass immunization campaigns. Many other immunizations were administered in the offices of private physicians. Private physicians give about 70 percent of all immunizations in California.

Several counties carried out community-wide immunization campaigns. Wherever such campaigns were held during the fall and winter of 1966-1967, a dramatic decrease in the incidence of measles was noted in 1967. The incidence of measles did not decrease in communities which did not carry out measles eradication programs.

In spite of these efforts, however, there is still a large backlog of measles-susceptible persons in the state, including about one and a half million children under the age of ten. Approximately 354,000 newborns enter the reservoir of susceptibles each year.

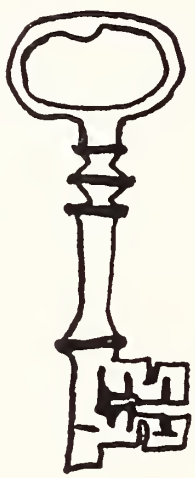
For the eradication of measles in California intensive immunization campaigns will have to be carried out in those areas which have not yet had campaigns, and in addition, continuing maintenance programs will be required to immunize infants at about one year of age. The recent enactment of legislation in California making measles immunization mandatory for first school admission will serve, as did the poliomyelitis legislation of 1961, as a screening device to identify young persons who missed immunization at an earlier age. These efforts will require the close cooperation of medical societies and local health departments. The most successful measles immunization campaigns of 1966 and 1967 were those in which local medical societies participated vigorously. This confirms earlier experience with the poliomyelitis campaigns. The dramatic success of these campaigns in practically wiping out poliomyelitis is

attributable in large part to the active role of the medical profession which was able to enlist the support and cooperation of the community.

With declining incidence of measles, it will be increasingly important to improve surveillance and reporting, to identify isolated cases and, where several cases occur, to determine whether or not they are related. Measles has consistently been under-reported in the past. Many children with the disease are not seen by physicians and physicians often neglect to report cases they do see. According to a survey conducted by the Bureau of the Census, an estimated one case in fourteen is all that is reported.

Careful surveillance of measles and its complications is necessary for effective evaluation of the statewide measles eradication program. This will make it possible to identify areas in which adequate levels of protection are not reached and to define groups for which epidemic control programs should be instituted. Although serious reactions to measles vaccine have been very rare, adverse reactions should be continuously reviewed and reported to local and state health officials.

Measles need no longer take its annual toll in death and disability among children. A single case should be regarded as evidence of failure on the part of the medical profession, public health authorities and parents to safeguard infants and children under their care. With the active cooperation of California's physicians, measles can be virtually eradicated in California.



NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

William C. Reeves, Ph.D., has been named **Dean of the School of Public Health** at the Berkeley campus of the University of California. Dr. Reeves had served as acting dean of the school since the death last 18 April of Dr. Charles E. Smith, accepting an administrative assignment in addition to his duties as Professor of Epidemiology at Berkeley. The new dean, renowned for his studies on the transmission of encephalitis, had lectured at the School of Public Health and the Medical School in San Francisco and had served as a research associate for the Hooper Foundation there before his faculty appointment to the School of Public Health in 1949. In addition to his campus service, Dr. Reeves is a consultant to numerous civic, state and national governmental agencies and to the major international health organizations.

LOS ANGELES

Southern California Psychiatric Society will hold its annual spring convention at the Ambassador Hotel in Los Angeles 20 April 1968.

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Los Angeles County General Hospital in East Los Angeles has been renamed the **Los Angeles County-University of Southern California Medical Center.** Reflecting an agreement between the county and the university, the County Board of Supervisors ordered the name changed to one "which more accurately describes its purpose."

In proposing the change in name, Supervisor Ernest E. Debs, representing the district in which the hospital is located, noted that "with the advent of Medicare and Medi-Cal, the character of the hospital has undergone a change from that of a facility limited to the care of indigents to a community-type hospital caring for private patients as well."

With the departure of the California College of Medicine to the UC campus at Irvine by 1 July, all the services at the hospital will be staffed by the USC School of Medicine faculty. Clinical experience on the wards and in outpatient clinics is now being provided for 281 USC medical students, as well as for the hospital's 202 interns and 350 resident physicians.

SAN FRANCISCO

A program dealing with **recent advances in** pediatrics will be presented May 9 to 11 at the University of California-San Francisco Medical Center. Advances in neonatology, cardiopulmonary disease, renal and electrolyte disorders, endocrine aberrations, gastrointestinal disorders, human chromosomal abnormalities and infectious diseases will be discussed. Principal speaker will be Dr. C. Henry Kempe, Professor and Chairman, Department of Pediatrics, University of Colorado Medical Center, Denver.

Information may be obtained from Continuing Education in Health Sciences, University of California San Francisco Medical Center, San Francisco 94122.

SANTA CLARA

Dr. John A. Luetscher, Jr., professor of medicine and head of the division of metabolic diseases and endocrinology at Stanford University School of Medicine, has been presented the **Mayo H. Soley Award** of the Western Society for Clinical Research.

The award, which was established shortly after the death of Dr. Soley in 1949, is presented for "outstanding research work to a worthy investigator of the West." Dr. Luetscher is the first recipient of the honor which was presented at the Society's annual meeting in Carmel 2 February.

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The officers of the **Santa Clara County Radiological Society** for 1968 were announced as follows: President, Dr. Robert H. Reid; President-Elect, Dr. Charles L. Rennell; Treasurer, Dr. Harold P. Lipton; Secretary, Dr. D. Brendan O'Donnell.

YOLO

A number of **appointments to the faculty** of University of California, Davis, School of Medicine have been announced during the past month:

Dr. Reed M. Nesbit, professor of surgery and urology at the University of Michigan Medical School, has been named special assistant to the dean and lecturer in surgery. Dr. Nesbit is 1968 president of the American College of Surgeons, was president of the American Association of Gastro-Urinary Surgeons in 1959-60, and is a past president of the North Central Section, American Urological Association. This year he serves as chairman of the Joint Commission on Accreditation of Hospitals.

Dr. Loring F. Chapman has been appointed professor and chairman of the department of behavioral biology. Dr. Chapman, who holds a Ph.D.

degree in biopsychology from the University of Chicago, comes to Davis from the National Institutes of Health where he was chief of the behavioral biology branch of the National Institute of Child Health and Human Development. He was also clinical professor of pediatrics at Georgetown University Medical School.

Dr. Douglas D. Vollan has been named coordinator for Regional Medical Programs (RMP) in heart disease, cancer, stroke, and related diseases. Dean C. J. Tupper said that Dr. Vollan will assume responsibilities for RMP in the 23 Northern California and Nevada counties covered under a planning grant to Davis from the Division of Regional Medical Programs, National Institutes of Health. RMP is organized in California around the state's eight medical schools.

Other appointees and the posts they will occupy at Davis are as follows:

Dr. Nemat O. Borhani, former chief of the bureau of chronic diseases of the State Department of Public Health — chairman of the department of community health and professor of internal medicine.

Dr. Robert S. Stempfel, Jr., professor of pediatrics and associate professor of physiology at Duke University School of Medicine — professor and chairman of the department of pediatrics.

Dr. Louis W. Conway, associate professor of neurosurgery at the Medical College of Virginia — assistant professor of neurosurgery.

Dr. Antonio Zappala, professor and chairman of the departments of anatomy and neuroanatomy at the Federal University of Pernambuco, Brazil — associate professor in the department of human anatomy.

Dr. Nanine Henderson, an NIH Postdoctoral Fellow in the laboratory of chemical biology of the National Institute of Arthritis and Metabolic Diseases — assistant professor in the department of human anatomy.

Dr. Robert E. Smith, assistant professor of physiology and biophysics at University of Kentucky College of Medicine — assistant professor of physiology.

Dr. G. Henry Schmitt, assistant professor of pharmacology at Kentucky — assistant professor of pharmacology.

Dr. Thomas L. Volk, assistant professor in the department of pathology and oncology at the University of Kansas Medical Center — assistant professor of pathology.

Dr. Lois F. O'Grady, a hematologist specializing in research on blood cell formation in transplanted bone marrow — instructor in internal medicine.

GENERAL

Dr. Samuel R. Sherman, San Francisco, has been elected vice-chairman of the Council on Legislative Activities of the American Medical Association.

Dr. Leon P. Fox, San Jose, has been appointed a member of the Committee on Nursing, and **Dr. Malcolm S. M. Watts**, San Francisco, has been appointed a member of the Committee on Planning and Development.

Reappointments of other California physicians to committees of the AMA were announced as follows:

Dr. Packard Thurber, Jr., Glendale — Council on Occupational Health.

Dr. James C. Doyle, Santa Monica — Committee on Medicine and Religion.

Dr. Donald W. Petit, Pasadena — Committee on Continuing Medical Education.

Dr. Stuart C. Knox, Los Angeles — Council on Mental Health.

Dr. Leopold J. Snyder, Fresno — Council on Rural Health.

Dr. Ernest E. Simard, Salinas — principal representative of the College of American Pathologists on the American Medical Association's Interspecialty Committee for 1968.

Dr. C. I. Barron, Burbank — Committee on Aerospace Medicine of the Council on Occupational Health.

Dr. Vernon L. Nickel, Los Angeles — Committee on Rehabilitation.

Dr. Charles B. Hudson, Oakland — Council on National Security.

Dr. Charles H. Hine, San Francisco — Committee on Medicolegal Problems.

Reappointed to the **Physicians' Advisory Committee on Television, Radio and Motion Pictures** were Drs. William F. Quinn and S. Mark Doran, Los Angeles; Richard H. Watt (co-chairman), and Leonard M. Asher, both of Beverly Hills; Wilbur G. Rogers and Louis J. Fisher, Glendale; Martin E. Hansen, Newport Beach; Gerald W. Shaw, Santa Monica; and M. B. Corbett, Pasadena.

The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 66 of the Advertising Section.

ABNORMAL SEXUAL DEVELOPMENT—A Genetic and Endocrine Approach to Differential Diagnosis—Daniel D. Federman, M.D., Assistant Professor of Medicine, Harvard Medical School; Associate Physician and Chief of Endocrine Unit, Massachusetts General Hospital. Illustrated by Sidney J. Rosenthal. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 206 pages, $8.75.

This fine, thin book, carefully crafted by author, illustrator and publisher, contains a concise, readable but thorough statement of the two major aspects of abnormal sexual development, the genetic, affecting the primary development of the gonads, and the endocrine, the development of the secondary effects of gonadal (and adrenal) function.

The chapter on differential diagnosis in the infant at birth is easy to follow to a logical conclusive diagnosis, and those on problems in the pubertal "female" and "male" are rewarding. The chapter on therapy is brief but then this is a book on diagnosis. The reviewer recommends that this book be read (two evenings will do it) by all pediatricians and urologists.

FRANK HINMAN, JR., M.D.

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LABAT'S REGIONAL ANESTHESIA—Techniques and Clinical Applications—Third Edition—John Adriani, Professor of Surgery, Tulane University School of Medicine; Clinical Professor of Surgery and Pharmacology, Louisiana State University School of Medicine; Director of the Department of Anesthesiology, Charity Hospital, New Orleans. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 565 pages, $14.00.

Few medical books applicable to modern day clinical medicine have the enduring excellence to be considered classic texts. *Labat's Regional Anesthesia* has been such a classic, and is now revised and brought up to date quite admirably by Doctor Adriani. Originally a surgeon's handbook, it contained outstanding diagrams and plates which have been retained in this new edition.

Being popular at a time when the senior members of a specialty of anesthesia were learning their basic principles, the Labat name and style are remembered fondly. If not for the death of the author, Gaston Labat, over 30 years ago, numerous revised editions would most certainly have bridged the gap since 1928.

In order to provide a "LABAT" for those who choose to have a classic, the original format and style are closely followed. In order to provide a clinically usable text, however, Doctor Adriani has attempted to delete the obsolete and add newer techniques and methods. Because of this dual purpose, the book is limited in its presentation of the step-by-step methodology the student of regional anesthesia tends to require.

On the other hand, the book is particularly easy to read. Chapters on the local anesthetic drugs, blocking of the autonomic nervous system, and non-surgical uses of regional anesthesia are included. Little-performed blocks such as of the Gasserian ganglion are also described.

One can be a bit critical, however, of the fact that procaine is the only local anesthetic mentioned in the sections on technique. Even in the chapter on local anesthetic drugs, the importance of the newer agents is not emphasized. Proper emphasis is also lacking in the description of certain blocks. As an example, the posterior, anterior, and paratracheal approaches for a stellate ganglion block are described in equal detail with only the statement that the paratracheal approach is the most popular today. The budding regional anesthesiologist certainly could use a bit more specific direction when attempting such a block.

All considered, this volume would be a valuable addition to the library of any practitioner requiring a knowledge of regional anesthesia. The neophyte, however, might do well to read this volume, but use some other text, where specific directions and guidelines are better elucidated, when attempting any specific nerve block.

MARTIN H. LIEBOWITZ, M.D.

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GYNECOLOGIC OPERATIONS — Indications, Technic and Results—Otto Kaser, M.D., Professor of Obstetrics and Gynecology, University of Frankfurt, Germany; and Franz A. Iklé, M.D., Associate Gynecological Surgeon, Canton Hospital, St. Gallen, Switzerland; English Language Edition by Albert Davis, M.D., F.R.C.S., Gynecological Surgeon, King's College Hospital Group, London, England, with Renate Marie Davis, M.B., B.S., London, England. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1967. 378 pages, $37.50.

This book is well written and well illustrated. The full title is accurate and informative. That is, the authors concern themselves with some discussion of most of the gynecologic conditions which might be treated surgically. It is by no means a manual of gynecological operations. One does not find here a detailed, step-by-step description of every gynecologic operation, with each step carefully illustrated. On the other hand the authors have obviously had extensive experience and have many helpful suggestions in the text. For example, their comments concerning the usefulness of various abdominal incisions are very well taken. The suggestions that one wear magnifying lenses in performing tuboplasties and warnings about which steps in the dissections are most likely to encounter bleeding are most helpful. Many of the operations are illustrated extensively and these are very well done.

An attempt has been made to cover the field very broadly but this is not possible in a volume of this size —particularly since the authors' own interests have heavy emphasis. Thus approximately fifty pages are devoted to operations for carcinoma and these operations are de-

scribed in great detail. Endometriosis, however, is covered in two paragraphs with no illustrations. Ovarian tumors are covered in only a few pages. Approximately seventy-five pages are devoted to urologic and proctologic procedures. Obstetric operations such as cesarian section and operations for the incompetent cervix are included. An attempt is made to cover such subjects as bowel adhesions, bowel damage at surgery, and colostomy.

The section on urologic and proctologic procedures contains an excellent discussion of stress incontinence of urine. The factors responsible are clearly presented. The variety of procedures employed for correction are well covered. A frank discussion is given of results to be expected, particularly over some period of time following the surgery.

In my opinion this text would be most helpful to those already familiar with gynecologic surgery—as the authors suggest in the foreword. It is not for those seeking an introduction to these operations. To those of some experience it will be most helpful because the authors comment freely upon the practical usefulness of the many techniques considered. They have many helpful hints concerning the details of the operative procedures and they leave an accurate impression of the results obtained in their hands as well as the drawbacks they have encountered.

WILLIAM J. DIGNAM, M.D.

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ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY—Fourth Edition—E. Grey Dimond, M.D., Member, Scripps Clinic and Research Foundation, La Jolla, California; formerly Professor of Medicine, University of Kansas, Lawrence; Past President, American College of Cardiology. Little, Brown and Company, 34 Beacon Street, Boston, Mass. (02106), 1967. 152 pages, $7.50.

Dr. E. Grey Dimond again presents "Electrocardiography and Vectorcardiography" as "blackboard electrocardiography." His reputation as an outstanding teacher is upheld and enhanced by this 4th edition. The format and illustrations are clearer and more attractive than in the previous work, and references are now available at the end of most of the chapters. Also reproductions of electrocardiograms are now more sharply defined. Many of the diagrams have been revised, thereby enhancing their value. A chapter on "Challenges To Electrocardiography and Vectorcardiography" has been introduced in an attempt to give a perspective to the field as it exists today. It is short, controversial, interesting and challenging.

The final chapter on "The Electrocardiogram During And After Exercise" is excellent and affords the seasoned clinician, as well as the beginner, a top-notch frame of reference for interpretation of exercise tolerance tests.

Unfortunately the author has seen fit to delete the previous "Glossary" section which was particularly valuable to the neophyte in the field. This was unique and will be sorely missed.

The chief criticism of the previous edition concerning the unfortunate separation of text and illustrations has now been corrected.

Minor points arise with which one might take issue, such as the statement that "left atrial enlargement characteristically affects the duration of the P waves." Many electrocardiographers would hold that broad P waves may be due to conduction delay proper. Therefore, broad P waves do not necessarily reflect atrial enlargement. And the author's concept of the "juvenile pattern" would not be universally accepted. Lastly, it is unfortunate that the Frank system is not discussed in greater detail than the Cube system since the former is more widely used today.

This book presents a difficult subject in a clear and concise fashion and, like its predecessor, maintains its worthiness and value for the undergraduate, the postdoctoral student, and the practicing physician. Dr. Dimond's goal of a text to be used for teaching and learning in the field of electrocardiography, not as a reference or for extended discussion of complicated details, has been achieved.

HILLIARD J. KATZ, M.D.

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DEEP THROMBOPHLEBITIS—Pathophysiology and Treatment—J. Alex Haller, Jr., M.D., Professor of Surgery, Robert Garrett Chair in Pediatric Surgery, The Johns Hopkins University School of Medicine; John and Mary R. Markle Foundation Scholar in Academic Medicine. Volume VI in the Series Major Problems in Clinical Surgery, J. Englebert Dunphy, M.D., Consulting Editor. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 130 pages, $8.75.

This book concerning deep thrombophlebitis is the sixth in the series, Major Problems in Clinical Surgery. Both pathophysiology and treatment of this disease are very well covered. In an authoritative manner, Dr. Haller makes a strong plea for thoughtful medical management and aggressive surgical therapy when indicated.

Emphasis is placed on the importance of thrombophlebitis as a source of great morbidity and occasional mortality. The different clinical syndromes are well defined. The monograph clearly and concisely outlines the management of a disease that is generally treated without much enthusiasm by both physician and surgeon.

The purpose of the monograph as stated by the author is "to bring into focus the acute and chronic problems of inflammation and thrombosis in the veins. Its specific objective is to correlate the pathophysiology with altered hemodynamics in acute thrombophlebitis and in the postphlebitis limb." Both purpose and objective are amply realized.

The book is highly readable and beautifully illustrated. The author draws on his own experience and publications as well as those of other authorities in the field.

There is an excellent review of the surgical techniques employed in the management of phlegmasia alba dolens and phlegmasia cerulea dolens. In this regard support for Dr. Haller's enthusiasm for an aggressive surgical approach awaits further documentation in the future.

This book is highly recommended for all physicians and surgeons who treat deep thrombophlebitis. Information gained from this monograph cannot help but improve patient care.

WILLIAM K. EHRENFELD, M.D.

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RORSCHACH'S TEST—Vol. II, A Variety of Personality Pictures—2nd Ed., Completely Revised and Rewritten—Samuel J. Beck, Ph.D., Professorial Lecturer, Emeritus, Departments of Psychology and Psychiatry, The University of Chicago; Staff Associate, Michael Reese Hospital, Chicago, Illinois; and Herman B. Molish, Ph.D., Director, Psychology Division, Abraham Ribicoff Research Center, Norwich Hospital, Norwich, Connecticut. Grune and Stratton, Inc., 381 Park Avenue South, N.Y. (10016), 1967. 440 pages, $9.75.

This volume represents a complete revision of the classic presentation by Samuel Beck, published in 1945, on the Rorschach. At that time the Beck two-volume series shared with Bruno Klopfer, the primary position as the two leading exponents of Rorschach science and Rorschach technology. At present this volume completely revises the early edition with some heavier emphasis not only on Rorschach theory but also empirical findings. The cases selected for the present volume are somewhat reduced in number, that is, some twenty-nine cases, as compared with the earlier volume which had forty-six cases. The cases are newly selected and the interpretations are clearly tempered by the additional sophistication in

psychology and the understanding of human behavior, and by greater sophistication in Rorschach technology.

More conspicuously, the second edition has some seventy-one pages devoted to Part II, "Critique and Problems of Research, A Survey." This reviews in detail research and findings on the Rorschach in the areas of intellectual functioning, ego functioning, the handling of affective experiences, and sensitivity to "dark and white" (such as shading and white space perception), as well as studies of significant differences in content. The survey is fairly comprehensive, but by no means a critical survey. Obviously, the authors are concerned with reviewing in detail those facts which are established regarding the efficacy of the Rorschach as an evaluation instrument, and by no means are concerned with a critical attack on it or on its validity. This certainly is reasonable and understandable considering the purpose and intent of the volume.

This volume is by no means a "cook book." The volume is clearly intended for more advanced study for students of the Rorschach, and those who wish to get a "learner's permit" should direct their attention to the Volume I, "Basic Processes." It would also appear to this reviewer that it would be difficult to use this as a way of becoming acquainted with the Rorschach without some supervised experience with a more sophisticated Rorschacher. It is an interesting volume for those who wish to become familiar with the approach and the frame of reference employed by the highly trained user of the Rorschach, but will be less than adequate as a comprehensive study of the current status of the Rorschach as an instrument in the psychological and behavioral sciences. The book is well-written, clearly laid out, and represents an excellent effort in the domain which it intends to pursue.

ALEXANDER C. ROSEN, PH.D.

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GYNECOLOGIC PATHOLOGY—Frederick T. Kraus, M.D., Associate Pathologist, St. Luke's Hospital; Instructor in Pathology, Washington University School of Medicine, St. Louis, Mo. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1967. 504 pages, $18.50.

Frederick T. Kraus is a pathologist and faculty member of the Washington University School of Medicine in St. Louis, Missouri. It is his aim in this new book on Gynecologic Pathology to emphasize those pathologic observations which are most helpful to the clinician in making a diagnosis, selecting the best form of treatment, and in evaluating prognosis. In this goal, he has succeeded admirably.

The book is divided into eleven chapters, eight of which deal with the pathology of the female reproductive organs. The initial section discusses the embryology of the female genital tract. There is one chapter devoted to extragenital lesions of the pelvis and another considers the pathology of the placenta. The inclusion of an entire chapter on retroperitoneal tumors of the pelvis no doubt is the result of the influence of Doctor Kraus' chief, Dr. Lauren V. Ackerman.

The narrative style of the book is clear, concise and eminently easy to read. It reflects the personality of the author, and, unlike most textbooks on gynecologic pathology, this is not a dry, technical account of the gross and microscopic anatomy of disease. There are clinico-pathological correlations of all the conditions of major clinical importance, and these discussions are, to this reviewer, the book's most attractive feature. They reflect the author's complete familiarity with many of the problem areas in clinical gynecology.

Of great value are the numerous and excellent illustrations. They demonstrate beautifully the points mentioned in the text and, even in black and white, the gross pictures as well as the photomicrographs are outstanding and obviously selected with great care. The use of electron microscopy in gynecologic pathology is a feature of this book which gives it added importance.

Another outstanding feature of this book is the reference section found at the end of each chapter. The bibliography contains the pertinent, up-to-date literature on each topic discussed, and this alone makes the book of considerable value.

It is exceedingly difficult to find fault with this book. The author admittedly has limited the scope of the book. If there is a deficiency, it lies in the rather brief space allotted to cytology. The serious student of cytopathology would find little in the text that would be stimulating. Nevertheless, the role of cytology in hormonal evaluation and in early cancer detection has been properly emphasized.

All in all, this maiden effort by Doctor Kraus to separate the pathological wheat from the chaff and to give the clinician "just the facts" is amazingly successful. The book deserves a place in every up-to-date gynecological library.

EDWARD C. HILL, M.D.

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HANDBOOK OF CONGENITAL MALFORMATIONS—Edited by Alan Rubin, M.D., Research Associate in Obstetrics and Gynecology, University of Pennsylvania School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 398 pages, $14.00.

This is an extremely good book—well worth the price (rather high) to practitioners, especially pediatricians, obstetricians and general practitioners. The editor has not made the mistake of enumerating congenital malformations simply under eponyms although these terms have been included, but has succeeded in listing under anatomical and physiological terms innumerable congenital defects. The indexing is excellent and there is also excellent cross reference so that one has no difficulty in running down information about some defect whether one looks for a descriptive title or a more commonly used eponym.

Each condition has a capsule description which is extraordinarily complete and tells almost everything that one would look for without making a real search of the literature. Along with a description there is mention of prevalence, associated anomalies, hereditary factors, treatment and outlook with one or more bibliographic references.

There is a genetic glossary which many physicians will find most useful in this rapidly developing field.

This volume appears to be most authoritative but its chief charm is the availability and succinctness of the information it presents.

EDWARD B. SHAW, M.D.

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A TEXTBOOK OF NEUROLOGY—Fourth Edition—H. Houston Merritt, M.D., Henry L. and Lucy Moses Professor of Neurology, Columbia University; Director of the Service of Neurology, Neurological Institute, Presbyterian Hospital; Vice President in Charge of Medical Affairs and Dean of the Faculty of Medicine, Columbia University. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. (19106), 1967. 844 pages, $15.00.

The previous three editions of "Houston Merritt" *(Textbook of Neurology)* have been widely accepted and used. This fourth edition is improved by both the introduction of recent advances and the abridging of previous long descriptions; e.g., the addition of the syndrome of progressive multifocal encephalopathy associated with malignant neoplasms and presumably due to one of the papova viruses, and the complications of new therapy, such as the effects on the nervous system by phenothia-

zines and contraceptive hormones; while the description of neurosyphilis, now an uncommon disorder, has been shortened, but continues to be one of the best clinical descriptions in the textbook.

This edition maintains the same style and orthodox presentation as its predecessors and as a textbook of its type and character is excellent. Its 844 pages are highly informative, containing a vast amount of facts. However, the medical student who seeks a textbook which reveals underlying principles and educative approaches to the Discipline will find this one lacking in these respects. Moreover, it is too large for the presentation of "core material" to students, but should be a good reference text for their extended reading. It is an excellent textbook for the Internist and Neurological Residents.

DONALD MACRAE, M.D.

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CLINICAL EXAMINATION OF THE JUGULAR VENOUS PULSE —Arnold L. Colman, M.D., Clinical Instructor, University of California School of Medicine; Adjunct in Medicine, Mount Zion Hospital and Medical Center; Staff Physician, Lagunda Honda Hospital and Rehabilitation Center, San Francisco, California. With a foreword by John J. Sampson, M.D., Clinical Professor of Medicine, University of California School of Medicine; Senior Physician, Mount Zion Hospital and Medical Center; Past President, American Heart Association, San Francisco, California. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Ill. (62703), 1966. 183 pages, $10.50.

This is a short, concise, comprehensive and interesting book. It covers 21 subjects about the jugular pulse in 108 pages and follows this with an atlas of tracings recorded in clinical practice. It has 140 references. The principal aim of the book is to present a comprehensive view of the jugular venous pulse, its mechanisms, and clinical usefulness. This aim is accomplished and the book should be of use to medical students, internists, and many cardiologists.

It also presents a new method for recording the jugular venous pulse at the bedside which utilizes a photocell adapter for a conventional electrocardiograph. The adapter proposed for this is homemade and the book could be improved by a more precise description of the component parts and their assembly. If tracings of the quality presented can be reproduced by other clinicians with an apparatus they can construct, the method should be a significant contribution to bedside medicine.

DAVID H. BLANKENHORN, M.D.

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ATLAS OF SURGICAL OPERATIONS—Vol. II—Robert M. Zollinger, Professor and Chairman of the Department of Surgery, Ohio State University College of Medicine, and Chief of the Surgical Service, University Hospitals, Ohio State University; formerly, Assistant Professor of Surgery, Harvard University, and Surgeon at the Peter Bent Brigham Hospital; and Robert M. Zollinger, Jr., Resident Surgeon at the Peter Bent Brigham Hospital and Arthur Tracy Cabot Fellow in Surgery, Harvard Medical School. Illustrations by Carol M. Woike. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1967. 188 pages, $20.00.

(This book has been designed to complement Zollinger-Cutler's Atlas of Surgical Operations, Volume I (3rd Ed., 1961, The Macmillan Co.). Whereas Volume I is concerned primarily with standard procedures, Volume II (herewith reviewed) presents the more complicated surgical operations that have come into common usage during the past few years.)

As the art of the craft of surgery has advanced in recent years allowing surgeons to perform far more complicated procedures, the need for a well illustrated and thoughtfully edited atlas dealing with these techniques has arisen. This atlas, at least in part, admirably fulfills this need.

The format is the same as that used in Volume I and the discussion of each of the thirty different procedures includes indications, preoperative and operative preparation, anesthesia, position, incision and exposure, and details of the procedure in a step by step manner. Ninety-three plates and 514 figures are utilized.

Techniques in thoracic surgery include pneumonectomy, lobectomy, esophageal resection, esophagocardiomyotomy, and transthoracic hiatus herniorrhaphy.

I think that the outstanding material presented, however, is that dealing with the less commonly encountered abdominal procedures. Among the problems in this category are total gastrectomy, pancreaticojejunostomy (Puestow-Gillesby procedure), pancreaticoduodenectomy, hepatic resections and portalsystemic shunts. These beautifully illustrated discussions are among the best I have seen and should be of great value to the practicing general surgeon and those in surgical training.

ARTHUR P. WEBER, M.D.

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FUNDAMENTALS OF NEUROPATHOLOGY—Second Edition—William Brooks Dublin, M.D., Pathologist, Laurel Grove Hospital, Castro Valley, Calif., Assoc. Clinical Professor of Pathology, University of California, California College of Medicine, Los Angeles. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, Illinois (62703), 1967. 478 pages, $24.50.

If this textbook is read from stem to stern, one finds an immense collection of facts easy to read. A clinician, however, who reads to see the pathologic changes explaining a part of the whole clinico-pathologic problem, may find readability a poor substitute for ready information. A textbook can be an excellent information retrieval system, but when designed for students or residents or internists without special knowledge, it best serves a purpose as a teaching vehicle when, not only are facts displayed but interest created by showing relationships. Thus the clinician, student or graduate, with a case of carotid thrombosis—a common clinical problem—finds a brief comment on thrombosis on page 44. This, in turn, refers to photographs on pages 373-375. But on these pages, which give cerebral changes in vascular conditions, no pathologic picture of what to expect in the major clinical situation looked for is presented. Knowing mucormycosis may have a neurologic presentation by carotid thrombosis, he will find mucormycosis described on page 119, but not referred to otherwise.

Multiple sclerosis is a disease of interest to all, and the CSF changes are more important to the clinician than the histology of uncommon cerebral tumors. The CSF phospholipids are discussed, but not the common criteria of activity, namely cells, protein and colloidal gold curve. The CSF gamma globulins are said to be increased, but the normal range is not given.

Elsewhere the cerebral spinal fluid pressure is given as 7.5 to 15 millimeters of mercury—a fact few clinicians know as they measure pressure straight into a manometer, using the fluid as its own measure, stating the pressure as normal under 180 mm of water (CSF). Muscle atrophies are discussed under disorders of obscure nature —some are of obscure nature and some not, but the problem of differentiation between myogenic and neurogenic atrophy and the recognition of definite myopathic entities by muscle biopsy has become the major research activity in many departments of neurology. This problem is very briefly dealt with and its value not clearly emphasized, the information from histochemistry and cytochemistry of muscle biopsy being essentially ignored.

For such reasons, this is not a suitable text for students.

In addition, it is too large and not designed to give the "core" of neuropathology taught in about 30 hours of instruction in a medical school. Moreover, it lacks teaching method in its approach.

As descriptive neuropathology, it has great merit. This, along with its excellent reference source and its illustrations, should make it very useful as a reference text.

DONALD MACRAE, M.D.

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LONG-TERM HEMODIALYSIS—The Management of the Patient with Chronic Renal Failure—Constantine L. Hampers, M.D., Director, Dialysis Facilities, Peter Bent Brigham Hospital, Instructor in Medicine, Harvard Medical School; and Eugene Schupak, M.D., Director of Renal Service, City Hospital Center at Elmhurst and Assistant Professor of Medicine, Mount Sinai Medical School, New York, N. Y. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1967. 181 pages, $9.75.

This is a valuable monograph on a rapidly changing and still very complex therapy. It presents a realistic appraisal of the current status of chronic hemodialysis therapy as well as providing a well referenced survey of the complex pathophysiology encountered.

I believe it will be a very valuable quick reference source for a wide variety of clinical questions arising in chronic dialysis patients.

The monograph strongly emphasizes the twin coil dialysis system which is what the authors have routinely used in therapy. It should be noted that other authorities in the field believe that the Kiil dialyzer with highly monitored delivery systems which permit over-night, unattended dialysis at home, is a superior approach. With the latter equipment, very different kinds of problems are encountered which are not considered here.

FRANK A. GOTCH, M.D.

* * *

FRENCH'S INDEX OF DIFFERENTIAL DIAGNOSIS—Ninth Edition—Edited by Arthur H. Douthwaite, M.D., F.R.C.P., Consulting Physician, Guy's Hospital, London; Honorary Consulting Physician, Horsham Hospital, Horsham. The Williams & Wilkins Company, Baltimore, Maryland (21202), 1967. 1034 pages, $24.00.

In his preface to the first edition (1912), Herbert French stated the purpose of his text: "to cover the whole ground of medicine, surgery, gynecology, ophthalmology, dermatology and neurology," however superficial such coverage must be. Arthur H. Douthwaite, the current editor, espouses a similar intent. Unfortunately the explosion of medical knowledge in the more than half a century between the first and ninth editions has greatly increased the significance and popularity of specialized textbooks discussing the pathophysiology of disease in depth, at the expense of the purely clinical index of signs and symptoms.

The organization of this book has changed little over the years. The major change in the current edition is the adoption of a computer-compiled index with the anatomical name of the symptomatic area indexed instead of the symptom ("pain in the back" is replaced by "back, pain in").

Although many of the discussions are consistent with current thinking, a number have been transplanted from edition to edition with little recognition of changes in incidence of disease and diagnostic methods (rheumatoid arthritis is not mentioned as an antecedent of amyloidosis, and the congo red test is presented as the major diagnostic test). The continued use of terms of historical interest only, and which rarely appear in modern literature, such as gastrostaxis, chronic catarrhal colon, confuses the student. In addition, no effort is made to arrange the material to emphasize the priority of diseases likely to be responsible for a specific symptom (over 128 causes of colic are listed; osteogenesis imperfecta and general paralysis of the insane are discussed as major causes of spontaneous fracture, whereas the more common metastatic disease is at the bottom of the list).

However, it is rare for a medical text book to survive over a half century. This survival attests to the fact that despite its shortcomings a reference of this type is very useful to the student interested in a comprehensive differential diagnosis based solely on history and physical examination. It should therefore be available in every medical library. It is likely to be of less practical value to the practicing physician seeking an approach to the solution of a difficult diagnostic problem.

MARTIN BROTMAN, M.D.

* * *

PATHOLOGY—3rd Edition—Stanley L. Robbins, M.D., Professor and Chairman, Department of Pathology, Boston University School of Medicine; Director of the Mallory Institute of Pathology of the Boston City Hospital, Boston, Massachusetts; Lecturer, Harvard Medical School and Tufts University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. Price: $20.50 Single Volume, 1434 pp.; $25.00 2-Volume Set: Vol. 1, pp. 1/698; Vol. 2, pp. 699/1434.

This third edition of a popular textbook has been considerably revised. Its aim of presenting pathology as an approach to the understanding of disease has been advanced by additions of chemical and ultrastructural contributions without dwelling upon controversial or unclear aspects of recent discoveries. New findings by electron microscopy, for example, have been used chiefly to amplify existing knowledge, and so the text remains fully intelligible to those who are not familiar with ultrastructural patterns. There is neither an overwhelming amount of detail nor an excessive amount of dogmatic assertion. Some unusual diseases have been omitted, and other processes whose nature is obscure, such as gastritis, have been given very brief consideration. A moderate number of illustrations have been well chosen and clearly reproduced. Color illustrations are lacking, but no significant loss results. A bibliography at the end of each section is short, emphasizing publications of basic importance and those that provide further pertinent citations.

The result is a readable, up-to-date text, still usable as a single volume, which should be very helpful to the beginning student in pathology or to the clinician who desires a practical way to survey current knowledge in this field.

ALVIN J. COX, M.D.

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CLAUDE BERNARD AND EXPERIMENTAL MEDICINE—Collected Papers from a Symposium Commemorating the Centenary of the Publication of **An Introduction to the Study of Experimental Medicine** and the First English Translation of Claude Bernard's **Cahier Rouge**—Edited by Francisco Grande and Maurice B. Visscher. Schenkman Publishing Company, Inc., One Story Street, Harvard Square, Cambridge, Mass. (02138), 1967. 210 pages, plus 120 pages appendix containing first English translation of THE CAHIER ROUGE OF CLAUDE BERNARD, Clothbound, $8.95, and paperbound, $4.95. (THE CAHIER ROUGE is also published separately, 120 pages, $4.95 clothbound.)

One of the most significant and influential works for the development of modern medicine is Claude Bernard's *An Introduction to the Study of Experimental Medicine.* In France, the United States, and elsewhere, the centenary of its publication was celebrated in 1965, not only drawing attention to a remarkable book but giving emphasis to its continuing significance in contemporary medical thought and research. In the United States the celebration took the form of a symposium held at the University

of Minnesota and the present work is a record of the event and the contributions made by a panel of distinguished participants.

The participants at the symposium review the continuing significance and influence of almost every phase of Claude Bernard's concepts and contributions. Reino Vistanen, Evangeline Olmsted, and D.C. Tosteson present papers of very high merit on this significance of Bernard's philosophy and generalizations on modern science and medicine. Owen Wangensteen analizes his work on digestion; Hebbel Hoff, Roger Guillemin, and Alfred Fessard present papers on his work on the vasomotor system and the physiology of nerve junctional transmission as elucidated through the use of curare, and F. E. Shideman pursues the further development of the use of drugs in elucidating physiological mechanisms. Joseph Larner reviews the state of our knowledge on glycogen from Bernard's discovery to our day. Bernardo Houssay considers the concept of internal secretion and James Pi-Sunyer follows with a discussion on Bernard's establishment of a general physiology dependent upon the physicochemical relations of the cell. Frederick Holmes and Franz Halberg pursue Bernard's enormously productive concept of the *milieu intérieur*. Finally, Hebbel Hoff, Lucienne Guillemin, and Roger Guillemin discuss and present the first English translation of Bernard's *Cahier Rouge,* the precious red notebook in which for many years he jotted down his ideas, experimental protocols, and reflections and which provides extraordinary insight into the workings of the mind of this great scientific genius.

Inevitably, as in most symposia, there is a good deal of overlapping of material and unevenness of quality in the various presentations. Nonetheless, the symposium is highly successful in exhibiting the continuing influence of this great scientist whose work still dominates so much of physiology, and whose concepts have immediate relevance.

These essays are worthy of the closest attention by all physicians concerned with the evolution of scientific medicine.

J. B. DE C. M. SAUNDERS, M.D.

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THE TECHNIQUE OF PSYCHOTHERAPY—Second Edition In Two Volumes—Lewis R. Wolberg, M.D., Medical Director, Postgraduate Center for Mental Health; Clinical Professor of Psychiatry, New York Medical College. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1967. In Two Parts, 1411 pages, including 68 pages of references and 37 pages of index, $29.75.

The two volumes (Parts I and II) constitute one of the most comprehensive reviews of the psychotherapeutic process. This new edition (the first one since 1954) reflects the vastly increased knowledge and the many changes that have occurred in techniques and applications of psychotherapy over the past 13 years.

In Part I, psychotherapy is defined and distinguished from other events and forces which may benefit individuals with emotional disorders. The varieties of psychotherapy, their ingredients, indications, and the ways in which they help patients are presented along with discussions of spontaneous cures and remissions, placebo effects, the results of psychotherapy, the importance of establishing goals and the therapist's personality.

Dr. Wolberg discusses the controversial question of who can, and should, do psychotherapy and the training that is recommended for a psychotherapist. There are chapters describing the conduct of the psychotherapeutic interview and even the physical surroundings in which treatment should be conducted. He describes the technique of the initial interview, the formulation of diagnosis, dynamics and prognosis. He discusses the practical arrangements, indications for consultation, and such problems as inadequate motivation, dealing with patients' questions and the structuring of the therapeutic situation. He goes into considerable detail on the therapeutic process including the use of dreams and phantasies, the uncovering of unconscious material and interpretation.

In Part II he continues with the handling of resistance to cure and transference problems, the management of interfering attitudes on the part of the therapist, and the 'working-through' process. Supportive and reeducative techniques are discussed along with behavior and conditioning methods.

The major part of the second volume is devoted to such topics as the use of group therapy, somatic therapies, hypnosis, short-term treatment, handling of emergencies and supervision, and covers the subjects of treatment failures and the psychotherapist in community mental health.

Dr. Wolberg has successfully avoided using highly technical language, has organized the many topics and aspects of the subject in a systematic way and has attempted through the use of extensive illustrative case excerpts to be as specific as possible.

The book is intended as a technical guide to the practical daily problem of dynamic therapy and should prove to be a very useful aid for physicians who are interested in a better understanding of the theory, techniques, goals and problems of psychotherapy.

NORMAN Q. BRILL, M.D.

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PROGRESS IN MEDICAL GENETICS—Volume V—Edited by Arthur G. Steinberg, Ph.D., Professor of Biology, Department of Biology, and Associate Professor of Human Genetics, Department of Preventive Medicine, Western Reserve University, Cleveland; and Alexander G. Bearn, M.D., Professor and Chairman of the Department of Medicine, Cornell University Medical College. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1967. 151 pages, $9.00.

This is the fifth volume of this annual series which reviews subjects of current interest in medical genetics. The present volume is the shortest in the series and is more clinically directed than the earlier ones in that four of the five chapters focus on specific diseases or syndromes. The chapters are written by recognized authorities. The quality and readability as well as clinical versus a more basic orientation vary with each chapter. The first chapter, entitled "Nature and Nurture" by Rene Dubos, gives emphasis to the *and* part of the title and contrasts it with the older controversy of nature *versus* nurture. This is an especially brief chapter concentrating more on the philosophical aspects of heredity and environment with some attention given to current problems such as world population. The author appropriately notes that man is not infinitely adaptable and that he may achieve some technical advances to which he may not be able to successfully adapt because of limitations in his biological heritage. The second and most extensive chapter is "The Thalassemias" by D. J. Weatherall. This is an excellent and comprehensive discussion of the current status of our understanding of these conditions with emphasis given to the genetic and molecular biological aspects. The large bibliography makes it possible for those who are interested to return to the original literature. The third chapter is entitled "The Porphyrias: A Genetic Problem" by J. Waldenstrom and B. Haeger-Aronsen. As noted by the editors in the forward to this volume, the porphyrias "comprise a group of diseases of remarkable complexity," this

article does not seem to make this subject less complex despite specific consideration of the clinical pictures, hereditary patterns, population genetics and biochemical genetics of the porphyrias. S. Sherlock discusses "The Genetic Aspects of Liver Disease Associated with Jaundice" in the fourth chapter. The presentation of several of the diseases is brief which may reflect the fact that in general these conditions have been poorly studied in regard to their genetic considerations. The final chapter, "Genetics of Muscular Dystrophy," by A. E. H. Emery and J. N. Walton is a clear discussion of these diseases. The current classification emphasizes the increasing number of different conditions which comprise the muscular dystrophies. These chapters represent current reviews by experts and thus can be profitably read by both physicians and geneticists. Generally, clinicians should not encounter much difficulty in following and understanding the genetics of the conditions discussed. As with most genetically determined diseases the conditions discussed are not especially common; however, the understanding of the pathogenesis of these conditions is important for those who wish to be informed of advances in modern medicine. The clinician should find the book of interest to read but probably will not elect to include it in a personal library unless he has special interest in the specific diseases or in medical genetics.

ROBERT S. SPARKES, M.D.

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SURGERY FOR ACQUIRED MITRAL VALVE DISEASE—F. Henry Ellis, Jr., M.D., Ph.D. (Surgery), F.A.C.S., Consultant, Section of Surgery, Mayo Clinic, and Professor of Surgery, Mayo Graduate School of Medicine, Rochester, Minnesota. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 299 pages, illustrated, $17.00.

This is a book which describes in detail the history of mitral valve surgery complete even with photographs of pioneers in the field, the preoperative assessment of mitral valve disease, operative methods, postoperative problems and long-term clinical results. The book is extremely well documented with extensive references. It is a book which was certain to be written, and Doctor Ellis has written it well. The author notes that any book of this type is out of date almost as soon as it leaves the publisher, and the very few paragraphs dealing with tissue valve replacement of the diseased mitral valve indicate how correct this prophesy can be. All in all this is an interesting book which should belong to specialists concerned with mitral valve disease whether at the diagnostic or therapeutic level.

NORMAN E. SHUMWAY, M.D.

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AMBROISE PARE—Surgeon of the Renaissance—Wallace B. Hamby, M.D., Head, Department of Neurological Surgery, The Cleveland Clinic Foundation, Formerly Professor of Neurological Surgery, University of Buffalo School of Medicine. Warren H. Green, Inc., 10 South Brentwood Blvd., St. Louis, Missouri (63105), 1967. 251 pages, $9.50.

Ambroise Paré (c. 1510-1590), the most celebrated surgeon of the sixteenth century, is regarded by some as the father of modern surgery. Indeed, Geoffrey Keynes contended that Paré by reason of his personality, humanitarian outlook, and independence of mind was, in fact "the emancipator of surgery from the dead hand of dogma." Certainly he personified the highest ideals of surgery.

Of his personality and attitude of mind we know a great deal, especially as revealed in his own writings and notably from his autobiographical *Apologie* written towards the end of his long and productive life. Although it is difficult to assess and evaluate fully the originality of his surgical contribution which would merit the outstanding position he has come to occupy in the history of surgery, he demonstrates, despite lack of a humanistic education, true kinship with the spirit of the late Renaissance through his intense desire for social and intellectual progress and realistic appeal *ab auctoritate ad rem.*

From the voluminous literature on Paré, the author has put together a lively and detailed account of the personal life of the master surgeon cast in the midst of contemporary political and social affairs. The account is strictly chronological following concurrently with descriptions of places and events associated with the peregrinations of a military surgeon in the train of the French forces during a most violent period in European history. Almost as counterpoint to the major conflicts are the staccato battles between barber-surgeons, surgeons of St. Come and physicians of the Faculté as they wrangled over rules, procedures and rights of publication affecting the personal surgeon to four kings of France and the foremost surgeon of the century.

If the story is told with a degree of unevenness due to the rigidities of the strict chronological approach and to some unevenness in style, the author can be forgiven since throughout he has been able to impart his own enthusiasm and affection for a fellow member of his own craft of surgery. Paré wrote his major works for the guidance and direction of young surgeons and apprentices in surgery. The young surgeon of today will find equal inspiration in Dr. Hamby's account of this great master of surgery.

J. B. DEC. M. SAUNDERS, M.D.

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TEXTBOOK OF MEDICINE (Cecil-Loeb) — Twelfth Edition — Edited by Paul B. Beeson, M.D., Nuffield Professor of Clinical Medicine, University of Oxford; and Walsh McDermott, M.D., Livingston Farrand Professor of Public Health, Cornell University Medical College. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. Price: $20.50, Single Volume, 1738 pp.; $24.50, Two-Volume Set: Vol. 1, pp. 1-835 pp., Vol. 2, pp. 836-1738 pp. DeLuxe Two-Volume set: paged as above, price $30.00 Set.

ROENTGENOLOGIC DIAGNOSIS — A Complement in Radiology to the Beeson and McDermott Textbook of Medicine—Vols. I & II—J. George Teplick, M.D., Clinical Associate Professor of Radiology, Hahnemann Medical College; Marvin E. Haskin, M.D., F.A.C.P., Clinical Assistant Professor of Radiology, Hahnemann Medical College; and Arnd P. Schimert, M.D., formerly Associate Professor of Radiology, Hahnemann Medical College. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. Volume I, pp. 1 through 514, Volume II, pp. 515 through 1198, $38.00 the set.

The 12th Edition of the Cecil-Loeb Textbook of Medicine in 40 years carries on in the tradition of excellence which has made it a prized possession of two generations of physicians. Again edited by Doctors Paul Beeson and Walsh McDermott it covers the many fields of disease while exploring in greater depth those conditions considered more important.

There are 169 contributors to this prestigious volume of 1738 pages. 226 of the articles are newly written and 57 are on subjects not included in the 11th Edition. There are major revisions of the sections on Diseases of Bone, Diseases of the Nervous System, Environmental and Physical Factors in Disease and Diseases due to Chemical Agents.

At the present time a new dimension has been added to this textbook. The editors and publishers have recognized the importance of and the need for roentgenography in the education of the modern physician. These are presented in two volumes of a new work entitled *Roentgeno-*

logic Diagnosis by Doctors George Teplick, M. E. Haskin and A. P. Shimert. Two thousand illustrations with accompanying text provide a comprehensive (although necessarily limited) survey of the radiographic findings associated with most of some 800 diseases discussed in the Beeson-McDermott *Textbook of Medicine*.

The arrangement of the illustrations follows the sequence of presentation of the parent *Textbook of Medicine*. Thus the diagnostic criteria for each disorder are discussed under the disease entity rather than under the classification of radiographic appearance. Chemical, physiological and pathological aspects of the diseases discussed have been omitted except when essential.

This, then, is an atlas of the radiologic appearance of diseases in their various phases of onset, progression and complication. It is a book designed primarily for practicing physicians and residents in medicine rather than for radiologists. The radiologist may well feel that the illustrations depicted are not sufficent to fully portray particular disease conditions. To do this would be impossible for the enormous number and variety of conditions outlined in the present text. Taken for what it is, this is a novel, interesting and valuable addition to the modern textbook of medicine.

EDGAR WAYBURN, M.D.

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DIAGNOSTIC CELL PATHOLOGY IN TISSUE AND SMEARS—Herbert E. Nieburgs, M.D., Associate Clinical Professor of Pathology, Mount Sinai School of Medicine of The City University of New York; Director, Cytology Laboratory, The Mount Sinai Hospital of New York; Consultant, Division of Cancer Control and Research, New York City Department of Health, New York; Consultant, Department of Pathology, City Hospital Center at Elmhurst, New York. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1967. 310 pages, 556 illustrations, $17.50.

This practical monograph defines cytopathology as the study of characteristic cell alterations observed in smears and tissue sections. The author accentuates the role of minute structures of cell nuclei in the various histopathologic changes of different disease states. After an introduction dealing with the structure and general behavior of cells, he elaborates the diagnostic applications of these pathologic criteria with particular reference to the uterine cervix and compares the fine morphologic cell changes in inflammatory lesions, hyperplasia, impaired cell maturation and neoplasia as observed in smears and tissue sections. A long chapter is devoted to systemic malignancy-associated changes (MAC) in cells adjacent to and distant from malignant neoplasms. The remainder of the work concerns cytologic techniques, particularly collection, preservation and staining methods, and hormonal evaluation of vaginal smears.

The monograph presents 153 photomicrographic plates (mostly excellent), a bibliography of 253 papers, and a glossary of terms frequently employed in this field. The volume should be extremely useful to pathologists and cytotechnologists, since it stresses the diagnostic aspects of cytopathology.

STUART LINDSAY, M.D.

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PRINCIPLES OF HEAD AND NECK SURGERY—H. Robert Freund, M.D., Clinical Associate Professor of Surgery, State University of New York, Downstate Medical Center. Appleton-Century-Crofts, Division of Meredith Publishing Company, 440 Park Avenue South, New York, N.Y. (10016). 337 pages, illustrated by Gottfried W. Goldenberg, $12.50.

The book is neither a comprehensive text nor a complete surgical atlas. An attempt has been made, however, to incorporate both features. Although the illustrations are technically adequate and artistic, they are not, in many instances, ideal for demonstrating surgical anatomy. In addition, several procedures are described with no supplementary illustrations. There are discussions of pre- and post-operative care, dental splinting, and reconstructive procedures. A rather comprehensive bibliography follows each chapter. The book will be of some assistance to those interested in certain fundamentals of head and neck surgery.

DAVID SACHS, M.D.

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CANCER OF THE BREAST (Major Problems in Clinical Surgery—Volume V)—John S. Spratt, Jr., M.D., Professor of Surgery, University of Missouri; Chief Surgeon, Ellis Fischel State Cancer Hospital; and Director Cancer Research Center, Columbia, Missouri; and William L. Donegan, M.D., Assistant Professor of Surgery, University of Missouri, and Director, Clinical Research Unit, Cancer Research Center, Columbia, Missouri. With contributions by Raul Mercado, Jr., M.D., Professor of Radiology, University of Pittsburgh; Carlos Perez-Mesa, M.D., Associate Professor of Pathology, University of Missouri; and Francis R. Watson, Ph.D., Associate Professor, Department of Community Health and Medical Practice, University of Missouri, and Associate Statistician, Cancer Research Center, Columbia, Missouri. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 322 pages, $10.75.

This monograph is one of a series on major problems in clinical surgery. The author is eminently qualified to discuss the subject of cancer of the breast, although it is a difficult one to encompass because of the many ramifications and sincere differences of opinion as to therapy. The author logically relies heavily upon the experiences of the Ellis Fischel State Cancer Hospital in addition to those of some of the outstanding clinics in the country.

The monograph is well organized and begins with basic anatomy, epidemiology, diagnosis and pathology. The remainder of the book is devoted to various types of therapy for breast cancer and the end results.

An excellent review of the subject is presented and there are references available to the reader. This monograph should be extremely valuable to the student, house officer, and practitioner alike.

DONALD E. WAGNER, M.D.

Medical History

California's "First" Medical Book

David Wooster's *Diseases of the Heart* (1867)

EDWARD SHAPIRO, M.D., *Beverly Hills*

DAVID WOOSTER[15] was born 25 June 1825, in Jasper, New York. He was named after a granduncle who was a general of the Revolutionary Army. While a medical student in Cleveland, he volunteered in the Mexican War, after which he returned to school and obtained his M.D. in 1849. He settled in Michigan, married, and practiced medicine.

The discovery of gold in 1848 put a madness on the nation that did not exclude the sedate professions. Physicians in such numbers emigrated to the West that California in 1858 could boast one doctor to every 147 residents. In New York, it was one to 610, in Ohio one to 465, in Maine one to every 884 persons.[12] One of the 1,500 doctors who followed the gold rush was 25-year-old Dr. David Wooster. After he crossed the plains to California in 1850, he settled near the Yuba River where he mined and practiced medicine. Three years later, his wife sailed around the Horn to join him. Sated with his mining adventure, Dr. Wooster established a medical practice in San Francisco in 1856, where gold nuggets had changed a village into an instant metropolis.

San Francisco at this time was sans a medical periodical.[5] The *San Francisco Medical Journal* had begun in January 1856, but had died after a single issue. The *California State Journal of Medicine* had succumbed in April 1857. Aglow with editorial evangelism, Dr. Wooster founded, with Dr. David Trask, and edited the *Pacific Medical and Surgical Journal,* which prospered from 1858 to 1917. He sat mightily in his editorial chair for four years. In the third number of the journal, he denounced a report by a Dr. C. before the state society meeting of the first cesarean section performed in California (and one of the few in the world where the mother survived). Wooster had been called in consultation and had consented to assist at the operation. "There is no doubt that an immense mistake was made in this case," blurted Wooster.[5] There was also no doubt in San Francisco that Dr. C. was Dr. Elias S. Cooper, who that year had organized the first medical college on the Pacific Coast. A year later, he started up his own journal, the *San Francisco Medical Press,* in which he called his defamer "a medical Judas." The label seemed apt, since in the unsuccessful malpractice suit the patient had brought against him, Cooper found Wooster testifying against him. Later he sued Wooster on grounds of perjury; lack of evidence resulted in a demurrer.[3]

The first publication on diphtheria[17] in the United States was a pamphlet printed for general medical use by Dr. Wooster two years after the

From the Cedars-Sinai Medical Center and the School of Medicine, University of Southern California.

Read, with additions, as the 24th George Dock Lecture at the Walter Jarvis Barlow Society, Los Angeles, 30 March 1967.

Submitted 24 March 1967.

Reprint requests to: 123 North San Vicente Boulevard, Beverly Hills 90211.

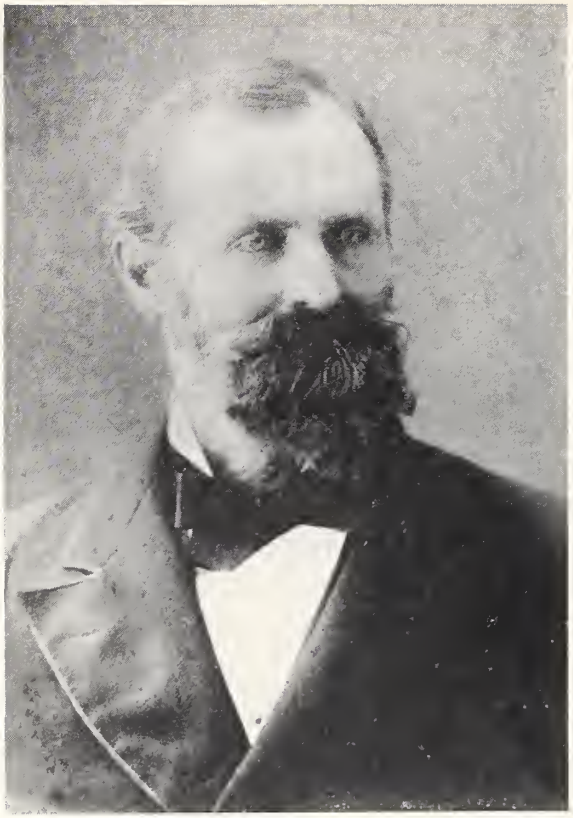


Figure 1.—David Wooster, M.D.

virulent epidemic of 1856 in the San Francisco Bay area.

Wooster's adventurous impulse soon overcame the advantages of a successful medical practice. In 1861, after enlisting in the U.S. Army, he became a major in the California Volunteers.[13] This organization of 1,800 soldiers was stationed at Fort Yuma, Arizona, to release regular troops for battle. Wooster, an uxorious man, was accompanied by his wife and his daughter Jean. One of his duties was to attend the nearby Indians. A certain Indian chief, fascinated with little Jean, enticed her to visit his tribe. The child's sudden disappearance from the fort created a panic which ceased only some days later when the chief returned the little girl. He explained that he had taken her with him to show her off to his family.

In 1863, Wooster resigned from the Army and returned to San Francisco. He was soon appointed U.S. Appraiser of Drugs and surgeon at the Marine Hospital.[1] He contributed frequently to the local medical journals.

A Malpractice Suit in 1872

For those who believe malpractice suits are a recent invention, let it be noted that Wooster was sued[3] for $30,000 in 1872 by one John Walter because of a poor result after a fracture. Wooster defended himself by showing records proving he was called in by Dr. Daniel Todd after two days and that the case was a difficult one. Wooster listed 67 visits; fee, $300.00. The jury verdict was for the plaintiff and gave damages of $1,100. Five years later, Wooster took to court Timothy Page for failure to pay a bill of $1,000 for treatment of his child's morbus coxarious. The defendant countered with a charge of negligence. The jury voted malpractice was not proved, and that Wooster be awarded his fee of $1,000 plus $365.50 in costs.

In 1862 and in 1880, Wooster[21] treated two patients with hyperthyroidism, and was the first in California to write on exophthalmic goiter. Consistent with the times, he considered the disease a disorder of the nerve ganglion with only incidental involvement of the thyroid gland.

For Bret Harte's *Overland Monthly* in 1871 Wooster[20] wrote "A Ride With The Apaches," prepared from the unpublished narrative of Jose Mendivil, a captive, who after seven years, stayed with the tribe. It is a description of the annual grand visit of the Apaches to the Zuñi tribe, "for the purpose of trade and talk . . . occasionally to get wives, or see a sweetheart secretly."

For some time Wooster suffered from heart disease[11] and on the morning of 20 September 1894 he warned his wife of his imminent death. That night, he died. The nature of his terminal illness and the accuracy of his prognostication call special attention to the title of his first book, *Diseases of the Heart, Their Diagnosis and Treatment.**

In a note printed in the program of a meeting of the Walter Jarvis Barlow Society a little more than a year ago, this book was spoken of as the first medical book published in California. The claim to primacy stems from a review that appeared in the Pacific *Medical and Surgical Journal*, California's only medical journal of the time. The reviewer wrote: "In our September number we noticed this work, which is, we believe, the first Medical Book issued from the California press."[1] In answer to inquiry in 1963, the California Historical Society[2] said that the question was re-

*A second book by Wooster, *Hip Joint Diseases*, appeared in 1876, according to his obituary in the San Francisco *Morning Call*, but it is not listed in the Surgeon General's Index Catalogue.

DISEASES OF THE HEART:

THEIR

DIAGNOSIS AND TREATMENT.

BY

DAVID WOOSTER, M. D.

MEMBER OF THE ROYAL ACADEMY OF MEDICINE AND SURGERY OF TURIN,
Assistant Surgeon in the "Mexican War," Surgeon (Major) in the late Civil War, Author of "Diphtheria and Congenital Asphyxia" (1859), Founder and former Editor of "The Pacific Medical and Surgical Journal," etc., etc.

SAN FRANCISCO:
H. H. BANCROFT AND COMPANY.
1867.

Figure 2. — Title page of California's "first" medical book.

ferred to Dr. Ludwig Emge, as an appropriate authority, and that he "has been unable to find any record of an earlier book in California on the subject."

Pretenders to Primacy

The claim that Wooster's *Diseases of the Heart* was first is not at all disturbed by two other possible pretenders. Dr. Roy Popkin has graciously given to the author a copy of Dr. L. J. Jordan's[9] *The Philosophy of Marriage, Being Four Important Lectures on the Functions and Disorders of the Nervous System and Reproductive Organs,* published in San Francisco in 1865. The introduction declares this the 47th (sic) edition. It is a vile tract against self-abuse, is full of case reports about lost manhood designed to frighten the young, and concludes with a pitch for treatment by correspondence at a fee of five dollars. The Surgeon General's *Index Catalogue* does not list it.

As to the other possible claim: a Los Angeleno of early days, one William Money,[10] known variously as Dr. Money, Professor Money and Bishop Money, in obviously planted newspaper articles referred to his forthcoming book *The California Medical Instructor* to be published in 1854, which he said would contain a list of 5,000 patients he had treated in 15 years, with only four deaths. The book is not listed in the Surgeon General's *Index Catalogue;* Dr. George Kress[13] expressed doubt it was ever printed, and W. W. Robinson,[14] Los Angeles' historian laureate, was of the same opinion. Therefore it appears historically founded that Wooster's book was indeed the first medical text in English published in California.*

Dr. Wooster's *Diseases of the Heart, Their Diagnosis and Treatment*[18] is a small pocket-sized book of 209 pages, a third as thick as *Lolita.* It was published in September 1867 by H. H. Bancroft, the noted San Francisco bookseller and historian. The book is not an original work; it is best described as a compendium. Writes the author in the preface, "I need not tell my intelligent readers that this treatise is merely an abstract; but it is hoped that they will find it what the author designed it to be, a careful and conscientious epitome of the knowledge now possessed by the profession on the subject of which it treats."

Wooster had been practicing medicine in California for eleven years when he wrote his book. He was busy — physician, editor, medical politician, and avid reader. "This work has been prepared during intervals of daily toil," he explains. He "freely consulted Walshe, Hope, Latham, Stokes, Bennett, Markham, Skoda, Rokitansky, Radcliffe, Brown-Sequard, See, Virchow, Claude Bernard, Flint, Piorry, and numerous other authors; also current medical literature of standard authority."

Why did Wooster compile this compendium? It is not unreasonable to conjecture that originally he made notes as he read his dozen favorite books on

*John B. de C. M. Saunders, M.D., has kindly pointed out to the author that "the first medical book to be published and printed in California is the anonymous *Botica General de los Remedios Esperimentados* issued at Sonora in 1838 as one of the 12 books of the Zamorano press. This work is of the greatest rarity. The only copies known in California are at the Huntington Library at Pasadena and in the hands of the heirs to Mr. Leo Carillo of Los Angeles. The copy formerly in the Bancroft Library at Berkeley was stolen. Two other copies outside of California are known (Boston and Streeter). . . . Although the *Botica* is of little consequence, nonetheless it is California's first medical book to appear in print. Of course, the first medical work to be published in California prior to the presence of a printing press, and hence not printed but circulated in the form of manuscript copies, is Father Prefect Sarriá's *Operacion Caesarea* written in 1830. Sarriá's work, a lengthy treatise on cesarean section, is the first published work *in sensu strictu,* and more significant in content than the *Botica.*"

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heart disease. His experience as founder and editor of the only medical journal of the time might have influenced him to take his manuscript to H. H. Bancroft, his bookseller, who was also a publisher. Is this groundless speculation? Was there a need for this book?

Wooster's Times in Journalism

What was the medical panorama of San Francisco like a century ago?[5] Although one medical school had foundered three years before, Dr. Hugh H. Toland's medical college was organized shortly afterward. In 1866, its museum and library were opened. Books were scarce; it would be two years before the transcontinental railroad would be completed to shrink the distance from coast to coast. So small was the medical college library that it was supported by one-dollar fines for tardiness at faculty meetings, two-dollar fines for non-attendance. Yet, by this time, the library of the Mechanics' Institute held more than 500 volumes.

The medical journal Wooster founded was the only one published for several years. There were seven hospitals in the city under national, municipal, religious, benevolent society and proprietary management. Wooster tells us that 500 physicians practiced in San Francisco at the time of his writing, in a population of approximately 75,000. It would not be until a year later that the San Francisco County Medical Society would be reorganized after it had dissolved five years before over uncompromising disagreement about fee schedules. Four years would go by before the American Medical Association would have its first meeting in the Bay city. A bill in the State legislature to regulate medical practice that had failed in 1865 would not pass until two years later. In this medically primitive San Francisco, a compendium of the current ideas in cardiology might be an asset to any thoughtful practitioner.

The scientific world of 1867 was likewise in ferment.[4] The awaited opening of the Suez Canal was the Sputnik of a century ago. From Glasgow, Joseph Lister had introduced antiseptic surgery. This stirred physicians as deeply as antibiotics did three generations later. The first Listerian laparotomy in San Francisco was performed in the patient's home where, Dr. O. O. Burgess[5] believed, there was less likelihood of infection than in the hospitals. Theodore Billroth was, to use Naunyn's phrase, making the abdomen the surgeon's playground.[4] Rokitansky and Virchow dominated the pathology of heart disease. Obsessed with the process of inflammation, they declared the cellular reaction around myocardial infarct betokened inflammation, and hence the disease was myocarditis. Since the coronary circulation was disregarded, these arteries were seldom mentioned in autopsy report.[3] The benefit of digitalis in heart failure was denied by Latham, Corrigan, Laennec, Stokes and Walshe.[2] In unsettled times like these, Wooster's sensible compendium in one's pocket or saddle bag could be helpful.

A Reviewer's Views

It is of interest to know how Wooster's peers considered his book. Seven months after its publication, it was reviewed by one J. H. H.[7] in the esteemed *American Journal of the Medical Sciences*. "His object," stated the reviewer, "has been to present to the profession a book in which the rules for diagnosis and treatment of diseases of the heart and aorta shall be clearly laid down. For the most part, we think, Dr. Wooster has attained his object. . . . The best authorities on diseases of the heart have evidently been freely consulted by our author. . . . To those who have neither time nor inclination to read the systematic treatises on diseases of the heart, this little work will give a very fair idea of the present state of our knowledge of the subject." Interspersed between these quotations are a few criticisms about hasty proofreading, and whether one quotation from Walshe is correct. Ten months later, Wooster[19] in the *Pacific Medical and Surgical Journal* mildly debated the reviewer's criticism, yet admitted "it is not the less a mistake, yet not a grave one." Although this journal in October 1867 had promised "we shall submit it to review in the next number,"[1] its review did not appear.

The first chapter of Dr. Wooster's *Diseases of the Heart* is a brief introduction. It encourages the San Francisco physician of 1867 — "I purpose . . . to show how simple it is for all educated physicians to say positively what portion of the heart is affected in most cases. . . ."

Chapter II, "Anatomical and Physiological Facts Concerning Location of Valves, and Origin of Heart's Sounds" describes the first and second heart sounds, and then ventures into the causation of the sounds. In an Appendix A, he adds material that for all the world sounds like the debate between William Dock and Aldo Luisada this very day — snapping of valves vs. tensing of the valves.

A later footnote says, "I do not venture to say that there is no other element in the causation of the first sound, but the closure of the auriculo-ventricular valves is the only cause of any practical importance." That adult, wealthy, dissipated city men are more liable to heart disease than women, children, peasants, the poor and those of regular habits is no new observation.

"Erotic Passion" and the Weaker Sex

"Courtesans," Wooster wrote, "rarely have disease of the heart! Excessive indulgence of the erotic passion, is, on the contrary, in men a great aid to the development of endocardial disease, and also of acute rheumatism, which is a conspicuous and very common forerunner of pericarditis."

Although he followed Rokitansky away from the concept of coronary disease that Edward Jenner knew — "Every acute disease of the heart is an inflammation"—he nevertheless went on to recognize that "it is disease of the heart . . . caused by atheromatous deposits, either alone or in company with cartilage and bone, with which we are most concerned." He said then that "we do not, and probably never can know why [calcium] is deposited in the heart at all."

Chapter III is devoted to "Diagnostic Signs of Endocarditis, Pericarditis, and Insufficiency of the Mitral Valve." "When there is a friction sound, persistent or no, there is pericarditis acute or chronic; and the disease is outside the heart." Then he goes on to describe murmur of mitral insufficiency — "the murmur will coincide with part or all of the first sound." He differentiates the radiation of aortic murmurs down the sternum from mitral murmurs that radiate into the axilla. The murmur is caused by "blood being repelled from the left ventricle into the left auricle through the imperfect mitral valve." He distinguished also the systolic murmur of aortic stenosis from the diastolic murmur of aortic regurgitation.

Case I in this chapter was that of a 20-year-old girl who was told by Dr.———— that, because of a murmur, she had incurable heart disease. Dr. Wooster was impressed by her pallor, "heart sounds distinct and *snappish,* that is, unusually definite. . . . She was assured she was anemic, and had no heart disease and was curable."

Case II was that of a woman with aortic stenosis. Wooster pointed out the path of his diagnostic thought and noted: "no jugular pulse, hence tricuspid not incompetent." He prescribed, after cupping and leeches, "digitalis occasionally for excessive rapidity of heart beats, . . . large quantities of bitartrate of potassa as a diuretic. . . . The object of the treatment is, in this case, to diminish the labor the heart has to perform, by guarding the integrity of the function of the [other organs], and last, but far from least of all, the nervous system, by preventing mental and moral disturbances. . . ." There follows a discussion of "intermittent pulse" which was then a wastebasket for the arrhythmias. He speaks of "precordial uneasiness in anemic subjects," saying that "there is every reason to believe this pain and the uneasiness are the results of defective nutrition of the heart itself."

Wooster's Views on Tobacco

Discussing treatment of mitral regurgitation, he said that "tobacco is very injurious to all kinds of heart disease"—as true today as in Wooster's time.

In Case III, the patient was a man with congestive heart failure from aortic and mitral valvular disease who was treated with iron, antimony, and digitalis. Wooster advises that "The passage of iron into the circulation and through the kidneys should be verified by adding gallic acid in urine . . . which if iron be present . . . will instantly become inky. Nothing is more fatal than the theory of treatment which proposes absolute rest in bed, with low vegetable diet for organic diseases of the heart."

Chapter IV is devoted to "Diseases of the Semilunar Valves of the Aorta, Direct and Regurgitant Murmurs—Differential Diagnosis of. Treatment of Disease of the Aortic Valves, and its Complications." An italicized quotation from Brown (one of the authors whose work Wooster had reviewed in preparation for his own), sounds the keynote of the section: "The time and localization at which the murmur is heard mark the lesion." Wooster emphasized that murmurs following the first heart sound are systolic, those following the second sound are diastolic. "All valvular diseases, in fact, all diseases of the circulatory apparatus, are, theoretically, likely to produce dropsy of the extremities. . . . The amount of edema of the extremities will be one of the measures of the degree of incompetency of the aortic or tricuspid mitral valves." (Wooster then refers to the Appendix C, Causes of Dropsy, and there he appears to have an inkling of the role of salt in edema. "Dropsy is caused by something more than mere venous or capillary obstruction," he declares. "The blood must become

deteriorated in albumen before true dropsy can take place. . . . It will be understood that dropsy is not an exudation of inflammation; the dropsical liquid contains no coagulable fibrin, and exudation does. . . . The diminution of albumen and increase of salts and water are rigorously coincident facts."

Wooster, further, noted that "pain in the region of the heart is an exceptional symptom in either mitral or aortic valvular disease."

Physical Signs in Diagnosis

Wooster constantly emphasizes physical diagnosis. "The hypertrophy of the heart that attends this disease is often very manifest to the naked eye, as well as to percussion. The ribs are seen to be sensibly higher over the left than right side; the heart's impulse is felt over a wider space, and more to the left, and longer. . . . I must not omit the sign pathognomonic of Dr. Corrigan: that is, visible pulses of all the superficial arteries. . . .

"The patient may eat a little at a time. . . . Small meals disturb the circulation much less than large. . . . If dropsy should occur . . . it must be met with purgatives, diuretics, and diaphoretics, that overloaded circulation which is its cause may be relieved as soon as possible; and to assist this purpose, absolute rest should be enjoined, and the heart's action diminished with small doses of digitalis, often repeated, or digitalis alternated with aconitine. . . . Digitalis has been objected to in many diseases of the heart by high authorities (Corrigan, Henderson, Walshe, etc.), and especially in aortic incompetency. . . . The more frequent the heart beats the less opportunity for regurgitation, and hence the less the ventricular engorgement; but digitalis slows the heart beats, and hence allows more time for aortic regurgitation. . . . Now, all this is true, but still is no objection to the guarded use of digitalis. . . . The drug should be given to slow an excited heart . . . but not to reduce it below 80 or 85. . . .

"The weight of the patient must be reduced from time to time by diminished diet, such as lean meat and dried meats, with a little stale bread, in small quantities, without vegetables or liquid food. Even water should be drunk sparingly. By these means the blood may be diminished in quantity . . . and at the same time its quality remain unimpaired. . . . The law applicable here is applicable in every organic disease of the heart. . . . The heart must be aided by diminishing the labor it has to perform, without diminishing its own proper vigor or functional ability."

Will our current treatises read as sensibly, in 2068, as Wooster's does today?

Of aortic stenosis, Wooster writes, "there is no known pathognomonic signs or signs of aortic constriction. Its existence may be made out with extreme probability, but never with the absolute certainty of mitral or aortic regurgitation. . . . A marked fact . . . is that the murmur is frequently heard in so many places and at such remote distances from its origin."

"Narrowing of the Aorta"

Under the heading of "Narrowing of the Aorta," Wooster describes what we now know as coarctation of the aorta. He quotes from Latham's description of a patient and from this description of Meckel's case: "The aorta was not more than half the diameter of the pulmonary artery. . . . These were evidently congenital malformations of the aorta."

Wooster then writes of angina pectoris: "Neuralgic pain, of which angina pectoris is undoubtedly an example, depends on some local anemia. . . ."

Sudden death as a complication of aortic insufficiency is stressed. "The patient drops dead without the slightest premonition. . . . The freer the heart is from any other lesion, Walshe says, the more likely is the patient to instant death from aortic regurgitation. The assurance of life is much longer if to the aortic, mitral regurgitation and ventricular hypertrophy be added. . . . Death occurs from syncope. It is a fainting away from which the patient never awakes."

Although we, 100 years after Wooster, think of aortic stenosis rather than aortic insufficiency as the prime cause of syncope and unheralded death, we forget the prevalence of syphilitic heart disease in Wooster's time, and we do not recollect that gummatous involvement of the ostia of the coronary arteries was a common cause of sudden death. Hence, as Wooster reminds us, the involvement of the mitral valve gives assurance of a longer life, because then the infection would be not the lethal spirochete but rheumatic fever.

Chapter V is entitled "Valves of the Pulmonary Artery, Constriction of the Mitral Orifice, Constriction of the Right Auriculo-Ventricular Orifice." Wooster quotes Skoda's declaration that he never observed disease of the pulmonary valve.

He cites Hope's creation of experimental pulmonic regurgitation "in the heart of an ass poisoned by Woorara" (curare). Mention is made of murmurs and thrills from the pulmonary artery compressed by tumor.

A Murmur at Moot

About constriction of the mitral orifice, Wooster and his British authorities find themselves contrary to American and current teaching. Latham wrote that a mitral diastolic murmur was a clinical curiosity, because the thin-muscled atrium had too feeble a contraction to create a murmur through the stenotic mitral orifice. And Wooster noted that "Markham met with less than a dozen cases in eight or nine years." Austin Flint, the only American author quoted in Wooster's book, says the mitral diastolic murmur "is by no means as rare as has been supposed." Nevertheless, Wooster's writing discloses a clear understanding of the pathophysiology of mitral stenosis. "This affection causes hypertrophy of the left auricle and right ventricle, pulmonary congestion . . . hemoptysis of venous blood frequent . . . breathlessness seen easily induced by over-exertion . . . Skoda's symptom, increased second sound of the pulmonary artery, is here well marked. . . ." Skoda heard the long diastolic murmur; however, Hope described it as "feeble, soft, usually on a lower key than a whispered *who.*" Skoda and Corvisart felt the thrill, as did Markham. Hope and Walshe never did feel a thrill in a patient with valvular disease. Wooster tells of a patient in San Francisco in whom "the thrill is indubitable; but it no more resembles the purr of a cat or the hum of a wheel than it does the filing of a saw—but it does accurately simulate the *thrill* felt by placing one's finger on a gum-elastic tube, a few lines in diameter, connected with a hydrant with the water turned on." The frequency of atrial fibrillation is mentioned: "A feeble, irregular, unequal, intermittent pulse."

The diastolic murmur of mitral stenosis was likely not heard by Wooster and his authorities because of the inefficient design of the monaural stethoscope of the period; low pitched sounds were well-nigh inaudible with Laennec's instrument. Also, we must remember that Duroziez did not describe the cadence of sounds and murmurs in mitral stenosis, *fout-ta-tá-rou,* until 1877, ten years after Wooster's book was printed.

Chapter VI is devoted to "Inorganic Murmurs — How Distinguishable from Organic-Diastolic Inorganic Murmur." In this chapter it is noted that "there are murmurs without valvular impediment, yet not without cause; but this cause is not always an impediment to the circulation." Wooster lists as inorganic murmurs the evanescent ones heard in convalescence from rheumatic endocarditis, after exercise, in children, and in chicken-breast; and he speaks of the cardio-respiratory murmur "in typhus, in cholera, in all exhaustive affections." Walshe is quoted as believing that short diastolic murmurs may be inorganic. Optimistically, Wooster concludes: "There is little doubt that one accustomed to auscultation of the heart would distinguish an inorganic from an organic murmur, in almost every case, by the mere quality, pitch, tone, strength, and duration of the murmur alone."

Chapter VII treats of "Pericarditis and Endocarditis. Endopericarditis—Carditis." "The characteristic sign of endocarditis is an endocardial murmur, systolic in time, occurring suddenly in a person with fever or acute rheumatism, in whom it had never occurred before." Wooster is well aware of rheumatic carditis. "The valves are sometimes rendered incompetent for a few hours or days only, and during this time a murmur of regurgitation—mitral—may be heard at the left apex," (this the Carey Coombs murmur) "or a diastolic murmur may be heard over the third left cartilage and thence down the sternum from incompetency of the aortic valves."

"Pericarditis is not known to be an idiopathic disease." This was long before the entity of idiopathic benign pericarditis was established by Barnes and Burchell in 1942. Wooster recognized that "it is chiefly the result of acute rheumatism," but he knew it could attend the severe infectious diseases, pyemia, pneumonia, and "rarely Bright's disease of the kidneys." Wooster saw it "with scurvy in three instances in the late civil war," and with "hepatic abscess of the left lobe—a case observed by the author at Fort Yuma in 1861, verified by post-mortem examination."

"The chief local symptom of pericarditis is pain (Walshe). . . . The pericardium is peculiarly insensible when inflamed, in Bright's disease. . . . Pericarditis is a much less frequent disease in warm than in cold climates, other things being equal. It is by no means so frequent in San Francisco as in Edinburgh or London." Wooster was probably the first to point out that rheumatic fever is a milder disease in southern areas. "In more than a hundred

cases of rheumatism treated by me in Arizona and Southern California during the years 1862 and 1863," Wooster says, "I saw but one in which I was able to verify that the inflammation had affected the heart." Then follows a case report of "acute endocarditis, apparently idiopathic, with emboli" in a soldier, age 25, who died after four days of illness that presented with cough. At autopsy done five hours after death, "the size of the heart and external aspect normal; no effusion in pericardium . . . nor congested coronary vessels. . . . The right auricle was completely plugged with a semi-organized looking clot. . . . The endocardium presented numerous signs of inflammation, especially about the auricles and valves; left auricle contained no clot; valves were competent. . . .

"The treatment of pericarditis and endocarditis . . . is essentially the same. . . . The diet must be diminished in quantity. . . . Blood may be taken from the arm, to the extent of a pound . . . and this may be followed by five, 10, or 20 leeches to the precordia. . . . The dose of propylamin, providing we are treating rheumatism with propylamin, may be quadrupled immediately. If the heart beats more than 90, half a drop of fluid-extract of digitalis and five drops of McMunn's elixir of opium may be given every hour until the pulse falls to 75 and increases in size and regularity. . . . If life is in imminent jeopardy by the accumulation of fluid in the pericardium, there can be no question of the propriety of tapping near the base of the heart, upper angle of fourth left interspace, and reinjecting a small quantity, of equal parts, tincture of iodine and distilled water, at the temperature of the blood to excite adhesion of the pericardial surfaces. . . . Iodine injections are recommended by Aran. . . . Seton at the precordia [and] mercurial inunctions . . . are seemingly beneficial. . . . Here passive exercise in the open air, and even sea voyages may be advised. . . . The trial of alkaline springs should be made, if possible."

A Precursive View of Cor Pulmonale

Chapter VIII deals with "Hypertrophy. Dilation." In it Wooster writes, "Obstructions in the lungs would cause hypertrophy of the right sooner than the left ventricle." This is a remarkable statement when one recalls that the concept of cor pulmonale is a product of the twentieth century. Wooster did not do bleeding indiscriminately, and his dietary regimen sounds modern. "A heart which will utterly fail to impel 16 or 17 pounds of blood—the normal amount—will get along with 14 or 15 pounds with little or no difficulty. It must not be inferred from this, that therefore bleeding to the amount of one or two pounds will answer the purpose. . . . If we wish to abstract a pound of blood from a patient with a dilated heart, we must do so by reducing the patient eight pounds in flesh, by means of low diet, or, in cases of urgent need, by total abstinence from food. . . .

"Dry cups to the heart in cases of extreme palpitation or angina often afford instant and enduring relief. Blood must rarely be taken. . . . The patient must lead a cheerful life, and not be exposed to annoyances and hardships. . . . No violent emotion or passion should be indulged. (Rupture of a dilated heart has occurred *in actu coitus.*) Animal diet is preferable; much drink of any kind, even if it be milk, is to be avoided. . . ."

Chapter IX takes up "Softening, Fatty Metamorphosis or Degeneration of the Heart, Rupture of the Heart. Cases." The author notes that "the diagnosis of softening of the heart is not easy nor absolute. This affection occurs in consequence of adynamic diseases, typhus, typhoid, diphtheria, variola, scarletina, etc." Wooster details the symptoms of softening as "feeble, irregular pulse; much diminished or absent first sound of the heart . . . the extremities presenting a leaden hue. . . . Such a case might be allowed moderate doses of whiskey or brandy, or half an ounce three times daily of a mixture composed of equal parts of cod-liver oil, whiskey, and syrup of wild cherry bark. . . .

"The diagnosis of fatty degeneration . . . is based on the symptoms already mentioned, to which may be added defective memory of recent events. . . . Respiratory forgetfulness is often observed." Is this not a reference to Cheyne-Stokes respiration? That Wooster used the microscope in necropsy is witnessed on page 157, in the description of a heart with fatty degeneration. "The heart was very soft, being easily rubbed to a pulp between the thumb and finger. . . . Examination under the microscope showed abundance of oil globules and amorphous pale muscular substance, but few striated fibrillae."

Aneurysm of the Sinus of Valsalva

On the next page is his report of the autopsy of a 30-year-old quadroon, "who died suddenly." "The beginning of aorta [the report notes] was atheromatous; the right coronary sinus was converted into an aneurysmal sac the size of a hen's egg." This is a graphic uncognizant description—the first

in the United States—of an aneurysm of the sinus of Valsalva, likely congenital, the first case of which had been described by James Hope[8] in 1839. By 1914, Smith[16] had found only 20 published cases. The first American case was reported 31 years after Wooster's.

Angina pectoris, described as "suffocative breast pang,[11] is a disease," Wooster wrote, "from which the poor are usually exempt. It attacks about nine males to one female. It rarely occurs before the fortieth year, seldom before the fiftieth. . . . No disease of the heart is more certainly recognizable than angina pectoris." Then follows a page of symptoms, the list and descriptions far inferior to Heberden's. But the pathologic anatomy does not fall into the error of Rokitansky and Virchow. "The coronary arteries," writes Wooster, "are frequently more or less ossified or constricted by atheromatous deposits." Wooster's physiology of angina pectoris follows Latham's—"The pain of angina . . . depends, then, on lack of supply of red blood to the heart itself, or upon impaired nutrition or irritation of that branch of the vagus which supplies the heart."

"Cooling It" for Angina a Century Ago

"But the most important part of the treatment of a subject of angina," Wooster continues, "is that directed to the postponing of the recurrence of the attack, which is sure to come again. . . . All emotional influences must be avoided. The temper must be controlled. The passions indulged with the greatest moderation. The natural calls of the body obeyed with deliberation. . . . There must be no violent or forced work, or exercise, or amusement." Dr. Wooster is not far afield for a century ago.

Chapter X is about "Thoracic Aneurysm: Diagnosis and Treatment. Cyanosis and Atelectasis." The discussion of signs and symptoms in consequence of the location of the aneurysm could fit in any present-day primer of physical diagnosis. When syphilis was rampant, even the pulmonary artery was sometimes, though rarely, a site of aneurysm. Wooster writes, "The disease is incurable . . . tracheotomy may temporarily prolong life when laryngeal symptoms threaten immediate suffocation."

Wooster's experience with and reading about cyanotic heart disease expose his inexperience. "Cyanosis is generally the result of a congenital defect in the heart," he begins. But then he lists open foramen ovale, patent ductus arteriosus, ventricular septal defect and pulmonic stenosis. Sensibly he admits, "but really the consideration of this disease hardly comes within my theme—it belongs to works on malformations of the heart, among which that of Dr. Peacock is excellent." Sound advice, applicable even today.

Chapter XI is a recapitulation headed "General Rules for Diagnosis of Diseases of the Heart." The second half of this chapter summarizes "General Principles of Treatment of Diseases of the Heart." The opening statement, partly italicized, is as pertinent now as a century ago. "The first and most important principle to be kept in view in treating a diseased heart is to diminish the labor it has to perform."

Chapter XII summarizes "General Reflections As To Prognosis in Organic Diseases of the Heart." In these pages, Wooster reminds the reader that "Insufficiency of the mitral valve, while it is the most common, is fortunately the least fatal . . . and the most controllable by systematic treatment. Mitral constriction if slight is not incompatible with tolerable health and long life; but when the constriction is considerable, its consequences follow in more rapid succession. Here the left heart remains unaffected, or may become atrophied for lack of work. . . . The blood, not being able to flow into the left ventricle in normal volume, accumulates in the left auricle, which hypertrophies; . . . part of its contractile force is expended backwards on the pulmonary veins . . . and so back to the right heart. . . .

"Disease of the aortic valves . . . is more lethal in tendency; and indeed less controllable by treatment. . . . Aortic obstruction . . . is more commonly met in middle or advanced age . . . and more frequently in males . . .; while females are more liable to mitral disease than to any other affection of the heart. . . . The narrowing of the aortic orifice to one-fifth its normal condition, is not incompatible with the continuation of life and the enjoyment of unsuspected health. . . .

"Acute pericarditis is seldom fatal. Acute endocarditis is somewhat more frequently fatal, but not more so than pneumonia. It almost always leaves disease of the valves. . . ."

Until the advent of cardiac surgery and the use of artificial or substitute valves, Dr. Wooster's words could be read with nearly as much profit as a century ago.

Addendum

While this paper was in preparation, Dr. Saul Jarcho published in the *American Journal of Cardiology* (16:881, 1965) "Cardiology After The Gold Rush (Wooster, 1867)," a brief discussion of the book. "Wooster found it necessary to define systole and diastole," Dr. Jarcho noted, "a fact which suggests that some California practitioners at this time were a little less than erudite."

"Presumably," he concludes, "this condition has been corrected."

ACKNOWLEDGMENT: My deep gratitude is due John Connor, Librarian of the Los Angeles County Medical Association Library, not only for his assistance, but also for his favor of directing me to a copy of Wooster's book for my own collection.

Appreciation for information goes to Neil S. Power, Supervisor of Taylor State Park, for permitting me in 1963 to study the papers of Dr. Wooster; to Allen R. Ottley of the California State Library; to Mrs. Helen S. Giffen, Librarian of The Society of California Pioneers; to W. N. Davis, Jr., Historian of the California State Archives; and to The California Historical Society.

REFERENCES

1. Anon.: Pacific Med. Surg. J., 1:220, 1867.

2. California Historical Society: Personal communication, 29 June 1963.

3. Davis, W. N., Jr.: Personal communication, 28 June 1963. (Historian, State Archives, Sacramento, Calif.)

4. Garrison, Fielding: History of Medicine, 4th Ed., W. B. Saunders Company, Philadelphia, 1929, p. 853.

5. Harris, Henry: California's Medical Story, Charles C Thomas, Springfield, 1932, p. 395.

6. Herrick, James: A Short History of Cardiology, Charles C Thomas, Springfield, 1942, p. 226.

7. H., J. H.: Review of Wooster's Diseases of the Heart, Amer. J. Med. Sci., 55:516, 1868.

8. Hope, James: A Treatise on the Diseases of the Heart and Great Vessels, 1st American Ed. from the 3rd London edition, Haswell & Johnson, Philadelphia, 1842, p. 437.

9. Jordan, L. J.: The Philosophy of Marriage, 47th ed., Frances & Valentine, San Francisco, 1865, p. 124.

10. Kress, George: History of the Medical Profession in Southern California, Times Mirror, Los Angeles, 1910, p. 13.

11. Obit.: Dr. Wooster Dead, *The Morning Call,* San Francisco, 21 Sept. 1894, p. 9, col. 1.

12. Pomeroy, Earl: History of the Pacific Slope, Albert Knopf, New York, 1966, p. 161.

13. Quebbeman, Frances E.: Medicine in Territorial Arizona, Arizona Historical Foundation, Phoenix, 1966, pp. 47, 49.

14. Robinson, W. W.: Personal communication, 2 Mar. 1967.

15. Rothwell, Bertha Stedman: Biographical Sketch of Dr. David Wooster, Daughters of The American Revolution, San Francisco, n.d., 8 pp.

16. Smith, W. A.: Aneurysm of the sinus of Valsalva, JAMA, 62:1878, 1941.

17. Wooster, David: An Essay on Diphtheria, with Cases, San Francisco, 1859, 32 pp.

18. Wooster, David: Diseases of the Heart, Their Diagnosis and Treatment, H. H. Bancroft, San Francisco, 1867, 209 pp.

19. Wooster, David: Aortic constriction, a question of privilege, Pacific Med. Surg. J., 3:413, 1869.

20. Wooster, David: A Ride With the Apaches, *Overland Monthly,* April 1871, pp. 341-345.

21. Wooster, David: Cited by Henry Harris, Ref. 5, p. 281.



The Carpal Tunnel Syndrome

A Review of 100 Patients Treated Surgically

JAMES R. DOYLE, M.D., *San Francisco*, AND
ROBERT E. CARROLL, M.D., *New York*

■ *The carpal tunnel syndrome, or compression neuropathy of the median nerve at the wrist, is a common cause of burning pain, numbness and tingling in the hand. The diagnosis is suggested by nocturnal paresthesias in the thumb, index and long fingers associated with signs of irritability of the median nerve in the carpal tunnel at the wrist. Surgical treatment in the form of incision of the transverse carpal ligament should be performed before irreversible motor and sensory changes occur.*

THE CARPAL TUNNEL syndrome, or compression neuropathy of the median nerve at the wrist, has been identified as a common cause of burning pain, numbness and tingling in the palm, thumb, index and long fingers.[8] This syndrome, as a manifestation of compression neuropathy, is probably more often encountered than neuropathies explained by the scalenus anticus syndrome, cervical rib or cervical disc disease.

The median nerve gains entrance to the hand from the forearm through an osseous canal which is covered by a firm inelastic transverse carpal ligament. It is at this level that it is so easily compressed by any condition which creates an increased volume in the contents of the tunnel. The carpal canal contains nine flexor tendons in addition to the median nerve. These tendons are surrounded by a synovial membrane which possesses great potential for inflammatory enlargement.

This study represents a review of 100 surgically treated cases of carpal tunnel syndrome over an 18-month period on the Hand Service at New York Orthopaedic Hospital under the direction of Robert E. Carroll, M.D.

Marie and Foix, in 1913, were the first to recommend decompression of the median nerve by sectioning the transverse carpal ligament.[7] This observation was made following the autopsy of a patient with pronounced bilateral thenar atrophy and neuroma of the median nerve proximal to the transverse carpal ligament. It was not until 1941, however, that Woltman performed section of the transverse carpal ligament for carpal tunnel syndrome.[11] He believed that the "median neuritis" which he observed was due to proliferation of the contents of the carpal canal which limited the space between the carpal bones and the transverse ligament.

Diagnosis

One of the earliest signs of the carpal tunnel syndrome is nocturnal paresthesia in the thumb, index and long fingers which typically appears two to three hours after retiring. These symptoms are

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usually relieved by vigorously massaging and shaking the hand. During the daytime, in addition to the paresthesias the patient may describe progressive weakness of pinch as manifested by "clumsiness" in the hands and dropping things. Prolonged grasp as in writing or ironing may initiate the symptoms.

The syndrome is usually seen in middle-aged women. In the present series 90 percent were females. The onset of symptoms usually occurred between the fifth and seventh decades. The age range was 15 to 87 years (Table 1).

In the 100 patients in this series the duration of symptoms varied from six weeks to fourteen years. The majority of symptoms were present six months or less. In most instances, the acuteness and magnitude of the symptoms prompted the patient to seek early relief.

A wide variety of occupations was noted in the cases studied but most of the patients were housewives (Table 2).

In the present series 38 percent of the patients had bilateral symptoms and in most cases the symptoms were more severe in the dominant hand.

A consistent physical finding (70 percent of cases) was that of hypesthesia of variable degree in the median nerve distribution.

Thenar atrophy was a less consistent finding but was recorded in 51 cases. (See Figure 1.) This thenar atrophy supports the subjective complaint of clumsiness or weakness in the hand. Thenar atrophy is considered to be a relatively late sign in this syndrome. If bilateral carpal tunnel symptoms are present with significant unilateral thenar atrophy, the side without the atrophy is operated upon first, since it is believed that irreparable damage may already have occurred on the other side.

Percussion over the median nerve at the wrist may produce an electric shock-like sensation into the thumb, index or long fingers if sufficient median neuritis is present. This test is best performed with the wrist in extension. This sensation was evoked in 85 percent of the cases studied.

Phalen described another valuable sign that can be evoked by acute wrist flexion.[8] The authors maintain both wrists in an acutely flexed position for 60 seconds. In this position the median nerve is compressed between the contents of the canal and the transverse carpal ligament. A positive response to this test is the production of numbness and tingling in the median distribution. Phalen observed that this test will not be positive if there is advanced sensory deficit in the median nerve distribution. The acute wrist flexion test was positive in 40 percent of the cases in the present series.

TABLE 1.—*Age Range of 100 Patients with Carpal Tunnel Syndrome*

Years	*Number of Patients*
15-19	2
20-29	4
30-39	7
40-49	21
50-59	35
60-69	17
70-79	9
80-87	5
Total	100

TABLE 2.—*Occupation and Sex of 100 Patients with Carpal Tunnel Syndrome*

	Female	*Male*
Housewife	65	
Garment Worker	11	
Maintenance Worker		1
Railway Porter		1
Nurse	4	
Staple Gun Operator	1	
Student	1	1
Book Binder	1	
Cashier	2	
Physician	1	1
Carpenter		1
Secretary	3	1
Waitress	1	
Sales Clerk	1	1
Electrician		1
Laborer		1



Figure 1.—Hands of a 57-year-old housewife with carpal tunnel syndrome on the left. Note the decided thenar atrophy and poor opposition in comparison with the asymptomatic right side.

Swelling along the volar aspect of the wrist often reflects proliferative tenosynovitis[6] and was noted in 10 of the 100 cases. This swelling was not necessarily associated with frank rheumatoid arthritis.

It is established that a compression or other compromise of a peripheral nerve will cause a delay in nerve conduction time when a given stimulus is applied proximally.[5]

Nerve conduction studies were employed in only nine percent of the cases in the present series. The authors did not find this test to be of great value since usually a decision could be reached from the history and physical examination. A normal nerve conduction test in one instance did not deter surgical intervention in the presence of a positive history and physical examination.

Pathogenesis and Etiology

In the earliest stages of this syndrome, compression of the median nerve beneath the transverse carpal ligament results in segmental hyperemia. In cases of long standing compression, actual indentation and constriction of the nerve occurs and a pseudoneuroma is often noted just proximal to the ligament (Figure 2).

It is generally agreed that the syndrome is the result of an increase in the relative volume of the contents of the carpal canal.[2,6,8,10] The flexor synovialis, usually a thin filmy layer surrounding the nine flexor tendons, possesses great potential for inflammatory response and consequent swelling and edema. Rheumatoid arthritis and so-called nonspecific tenosynovitis have been identified as the two most common causes of this inflammatory response. The great majority of cases appear to result from nonspecific synovitis of unknown cause.[6]

A variety of other conditions has been found in association with this syndrome.[1,3,4,9,11] Any condition which results in encroachment upon the space of the tunnel, such as rheumatoid arthritis, hypertrophic arthritis, carpal ganglia, gouty tophi, calcium deposits or anomalous low lying sublimis muscle bellies, may be associated with this syndrome in partial or complete causal relationship. The carpal tunnel syndrome is not an uncommon finding following Colles' fracture or carpal dislocations. Amyloid disease, acromegaly and myxedema have also been reported in conjunction with it (Table 3).

It has been suggested that venous congestion and stasis superimposed on an inflamed flexor synovialis or otherwise compromised tunnel is a prominent factor in the production of carpal tunnel symptoms.[2] Such vascular findings may accompany the relative inactivity of sleep and might explain the nocturnal occurrence of symptoms. The forceful manipulation and shaking of the hands which the patients resort to after being awakened probably alleviates the venous engorgement and thereby decompresses the carpal tunnel.

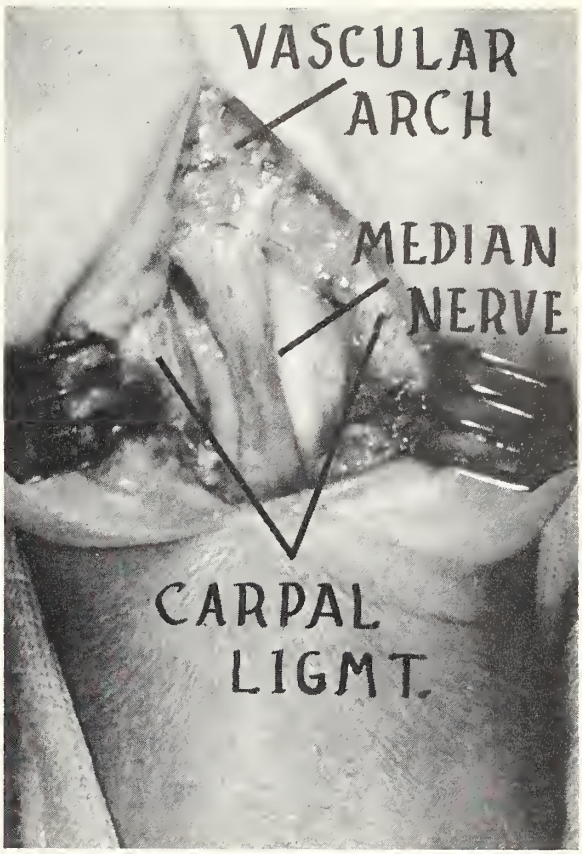


Figure 2.—Surgical exposure of the median nerve. Note the constriction of the nerve in its mid-portion. The transverse carpal ligament has been sectioned and is retracted to each side. Note also the superficial palmar vascular arch.

TABLE 3.—*Other Conditions Associated with Carpal Tunnel Syndrome (100 Cases)*

	Male	*Female*	*Total*
Rheumatoid arthritis	2	5	7
Trigger digits	4	33	37
Wrist ganglion		3	3
Dupuytren's		2	2
Colles' fracture or carpal injury	1	9	10
De Quervain's		6	6
Scleroderma		1	1
Embolism brachial artery		1	1
Diabetes	1	2	3
Prieser's disease		1	1
Sickle cell anemia		1	1

Treatment

Minimal forms of the carpal tunnel syndrome, as seen in patients who perform repetitive flexion and extension of the wrist, may well respond to simple change in physical activity. Patients who sleep with the wrists tightly flexed may benefit from the use of a night splint.[8]

Local instillation of hydrocortisone into the carpal canal around but not into the median nerve may also relieve symptoms. One milliliter of the steroid preparation is injected into the canal in the mid-line of the wrist with a short and small-gauge needle just proximal to the most distal wrist flexion crease.

These conservative measures are beneficial in patients with mild nonprogressive symptoms or in debilitated patients who are not to be operated upon. It should be appreciated, however, that these are temporary measures and do not usually afford a cure. Such conservative measures are to be condemned in the face of persistent symptoms which will invariably lead to neurologic progression and irreparable changes in the median nerve and thenar muscles.

Division of the transverse carpal ligament usually affords dramatic and immediate relief of symptoms. Complete decompression of the canal must be performed by total division of the transverse carpal ligament. The transverse carpal ligament attaches to the carpal navicular and greater multangular on the radial side and to the pisiform and hook of the hamate on the ulnar side of the wrist. With this orientation in mind it is obvious that an inter-thenar incision affords the best and most direct surgical approach (Figure 3). The authors strongly condemn the transverse wrist incision, as it does not allow adequate surgical exposure and in at least several instances of the senior author's experience has resulted in incomplete division of the ligament. Furthermore, such blind dissection has been observed to result in transection of the superficial transverse arterial arch with resultant palmar hematoma and skin slough and transection of the motor median (recurrent branch) nerve to the thenar muscles.



Figure 3.—The recommended inter-thenar incision. The dotted line represents a proximal extension which may be used if needed.

The procedure may be performed under general or regional anesthesia but a pneumatic tourniquet should be used in all instances. The palmar cutaneous branch of the median nerve should be protected but if severed care should be taken that its proximal end does not become incorporated in the scar, since this may result in bothersome postoperative dysthesias.

Following exposure of the carpal ligament, a curved hemostat is usually passed from the palm into and through the canal to the level of the wrist. A scalpel can then be used to cut down on the clamp without fear of cutting any of the underlying structures. Following section of the ligament, scissors may be used to spread beneath the subcutaneous tissues, and the forearm fascia is split proximally for a distance of about one inch.

The nerve is usually inflamed and it may be constricted beneath the mid-portion of the ligament (Figure 2). If a thickened perineurium is present, it should be excised. Usually the flexor synovialis is inflamed, edematous and of greater bulk than the usual filmy synovial covering. As much as possible of this abnormal synovium should be removed. The floor of the canal should be completely inspected since other lesions such as carpal ganglia may encroach upon the contents of the canal.

Before closure the tourniquet is released, and when this is done it is interesting to note the segmental hyperemia which is present in the portion of the median nerve lying beneath the ligament. Tanzer[10] advocates re-approximation of the transverse carpal ligament, but this we do not do in our procedure. A compression dressing is applied and left in place for seven to ten days. Finger and thumb motion is emphasized to the patient in the postoperative period.

Results

One patient was lost to follow-up after six months but was symptomatically improved at that time. The others were observed for a minimum of

one year. Two patients were symptomatically unimproved following operation. In one of them the area was reopened four months after the original procedure and a ganglion which was not evident at the time of the first operation was found arising from the bottom of the carpal canal. Complete relief of symptoms was achieved. The other patient noted persistent nocturnal paresthesias without obvious explanation.

All other patients were either completely relieved of symptoms or were significantly improved. It must be observed that in long standing cases of nerve compression with thenar wasting and distinct sensory deficits the bothersome paresthesias disappeared but muscle atrophy and objective sensory defects remained.

These observations should reemphasize the importance of early diagnosis and decompression of the canal.

In discussing the procedure with patients the surgeon may be confident in advising that the troublesome paresthesias will disappear. He should be more cautious in his comments about resolution of objective sensory defects and return of thenar muscle function. In the authors' experience, if thenar wasting had been present for over three years little or no return was likely.

Infection at the operative site occurred in one patient, a diabetic man. It was successfully treated with elevation, compresses and a broad spectrum antibiotic. It did not appear to alter or compromise the end result, which was considered to be good.

REFERENCES

1. Abbott, L. C., and Saunders, J. B. deC.: Injuries of the median nerve in fractures of the lower end of the radius, Surg., Gynec. & Obstet., 57:507, 1933.

2. Flatt, A. E.: The Care of the Rheumatoid Hand, C. V. Mosby Company, St. Louis, 1963.

3. Grokoest, A. W., and De Martini, F. E.: Systemic disease and the carpal tunnel syndrome, JAMA, 155:635, 1954.

4. Grossman, L. A., Kaplan, H. J., Ownly, F. D., and Grossman, M.: Carpal tunnel syndrome—initial manifestation of systemic disease, JAMA, 176:259, 1961.

5. Johnson, E. W., Wells, R. M., and Duran, R. J.: Diagnosis of carpal tunnel syndrome, Arch. Phys. Med., 43:414, 1962.

6. Lipscomb, P. R.: Tenosynovitis of the hand and wrist: Carpal tunnel syndrome, de Quervain's disease, trigger digit, Clin. Orthop., 13:164, 1959.

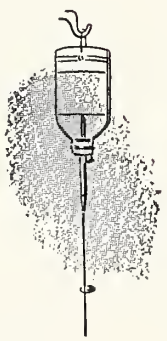
7. Marie, P., and Foix, C.: Atrophie isolee de l'eminence thenar d'origine nevritique: role du ligament annulaire anterieur du carpe dans la pathogenie de la lesion, Rev. Neurol., 26:647, 1913.

8. Phalen, G. S.: The carpal-tunnel syndrome, J. Bone Joint Surg., 42-A:211, Mar., 1966.

9. Schiller, F., and Kolb, F. D.: Carpal tunnel syndrome in acromegaly, Neurology, 42:71, 1954.

10. Tanzer, R. C.: The carpal tunnel syndrome, Clin. Orthop., 15:171, 1959.

11. Woltman, H. W.: Neuritis associated with acromegaly, Arch. Neurol. and Psychiat., 45:680, 1941.



Fatigue Fractures

JAMES M. MORRIS, M.D., *San Francisco*

■ *Fatigue (or stress) fracture of bone in military recruits has been recognized for many years. Most often it is a metatarsal bone that is involved but the tarsal bones, calcaneus, tibia, fibula, femur, and pelvis are occasionally affected. Reports of such fractures in the ribs, ulna and vertebral bodies may be found in the literature.*

In recent years, there has been increasing awareness of the occurrence of fatigue fractures in the civilian population. Weekend sportsmen, athletes in an early phase of training, and persons engaged in unaccustomed, repetitive, vigorous activity are potential victims of such a fracture.

The signs and symptoms, roentgenographic findings, treatment and etiology of fatigue fractures are dealt with in this presentation.

PAINFUL, SWOLLEN FEET in soldiers after long marches were first described in 1855 by Breithaupt, a German military surgeon.[6] He believed this condition was a traumatic inflammatory reaction in tendon sheaths and named it *Fussgeschwulst.*

Weisbach (1877)[14] believed that the lesion was in the ligaments and coined the term syndesmitis metatarsea. Pauzat (1887)[11] also pointed out its occurrence in soldiers and noted that there was palpable periosteal proliferation on the second, third or fourth metatarsals, the second being most common.

After these reports, other observers suggested various explanations of this lesion. In 1897, Stechow,[12] of the Prussian Guard in Madrid, using the newly discovered roentgen ray, defined the nature of the disorder. He reported on the roentgen examination of 36 patients and found that metatarsal fracture was the basic lesion. Many reports then followed; some investigators held that a fracture always occurred, while others noted that in a certain number of cases it did not develop. The descriptions of these lesions are now easily recognized to be of fatigue (march, stress) fractures.

It was gradually recognized that such fractures occurred in other bones. In 1905, Blecher[3] first reported on a case involving the femoral neck. Aleman (1929)[1] described a similar lesion in the tibia and Burrows (1948, 1940)[7,8] discussed cases of fatigue fracture in the fibula. Hullinger (1944)[9] reported on 53 cases of fractures of the calcaneus. In 1966, the author[4] reported on a series of femoral neck fractures which occurred in recruits undergoing basic training. Involvement in other areas, such as the ulna, humerus and ribs, has also been reported occasionally.

Relative frequency of involvement of various affected bones was obtained from a review of 700

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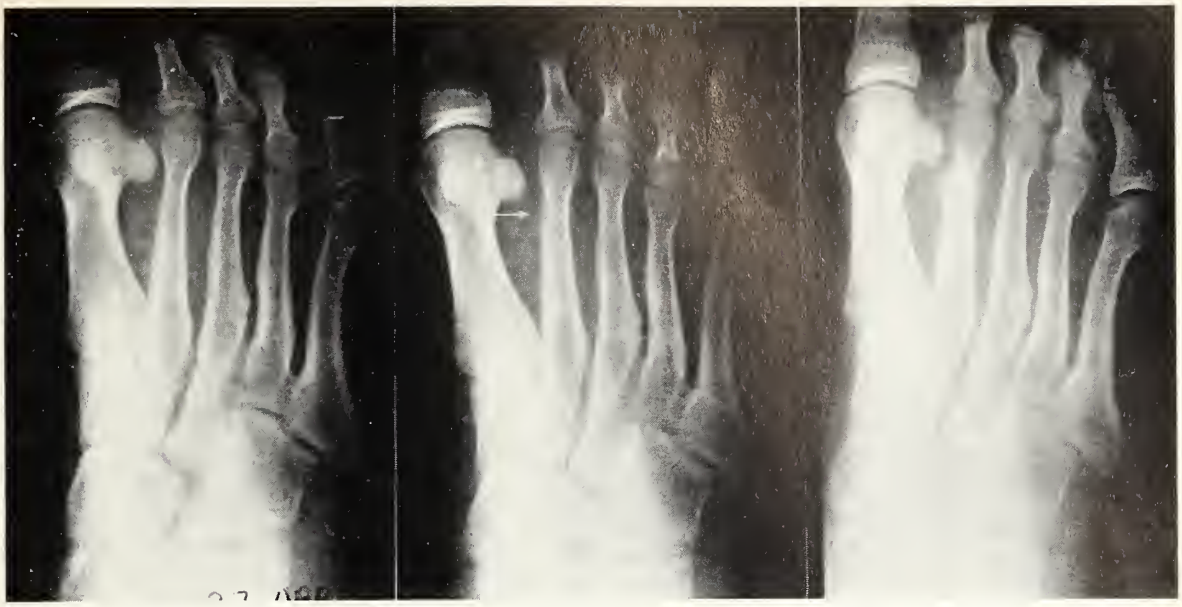


Figure 1.—Right forefoot of a 23-year-old recruit. Physical examination, approximately one week after onset of symptoms, revealed tenderness and swelling over the neck of the second metatarsal. Reading from left to right are: Initial x-ray film; ten days later, showing cortical crack (arrow) in the characteristic position in the medial cortex of the neck of the metatarsal; five weeks after onset of symptoms, showing callus formation.

cases of fatigue fracture which occurred during a three-year period at the Fort Ord Infantry Training Center. The incidence, expressed in per cent, was: Metatarsals, 51; calcaneus, 26; tibia, 17; femur, 4; fibula, 1; miscellaneous, including ischiopubic ramus, 1.

In the past, the lack of recognition of the true nature of the causative factors has led to a host of descriptive terms for this disorder. These include: swollen foot (Fussgeschwulst), syndesmitis metatarsea, march fracture, Deutschländer's disease, pied forcé, insufficiency fracture, overload fracture, wear-and-tear fracture, recruit's disease, periostitis ab exercitio, osteopathia itineraria, soldier's fracture, spontaneous fracture, pseudofracture, insidious fracture, creeping fracture, and stress fracture. Fatigue fracture is now considered to be the best descriptive term for this condition.

General Considerations

Fatigue fracture is a term used to describe three distinct but overlapping responses of normal bone to repeated minor stresses. A partial or complete fracture through the affected bone is the most obvious and well known response. The second is a microscopic fracture of bone which can be inferred to have taken place because of the subsequent callus formation or the later clinical progress of the disorder. The third response, a fatigue, or stress, reaction, is now being recognized with increasing frequency. In this condition, the affected area of the bone becomes osteoporotic; later, there is progressive development of endosteal and periosteal callus in response to continued activity. Apparently, timely curtailment of the inciting activity precludes the development of a true fracture.

Spontaneous fracture is a more general term which should not be used in referring to fatigue fracture, because a spontaneous fracture may occur either as a result of stress or fatigue of bone or in conjunction with pathologic disorders of bone. In a fatigue fracture, there is no evidence of systemic or local disease associated with any pathologic condition of the bone.

The general characteristics of fatigue fractures were described by Burrows in 1940:[8]

> Generally, involvement of the shaft of a long bone;
> Onset without violence;
> Frequently, association with prolonged muscle effort;
> Absence of any audible snap or of any suspicion by the patient that the fracture has occurred;
> Usually pain as the outstanding symptom;
> Liberal formation of callus and its subsequent development into mature bone;
> Presence of a variable degree of edema.

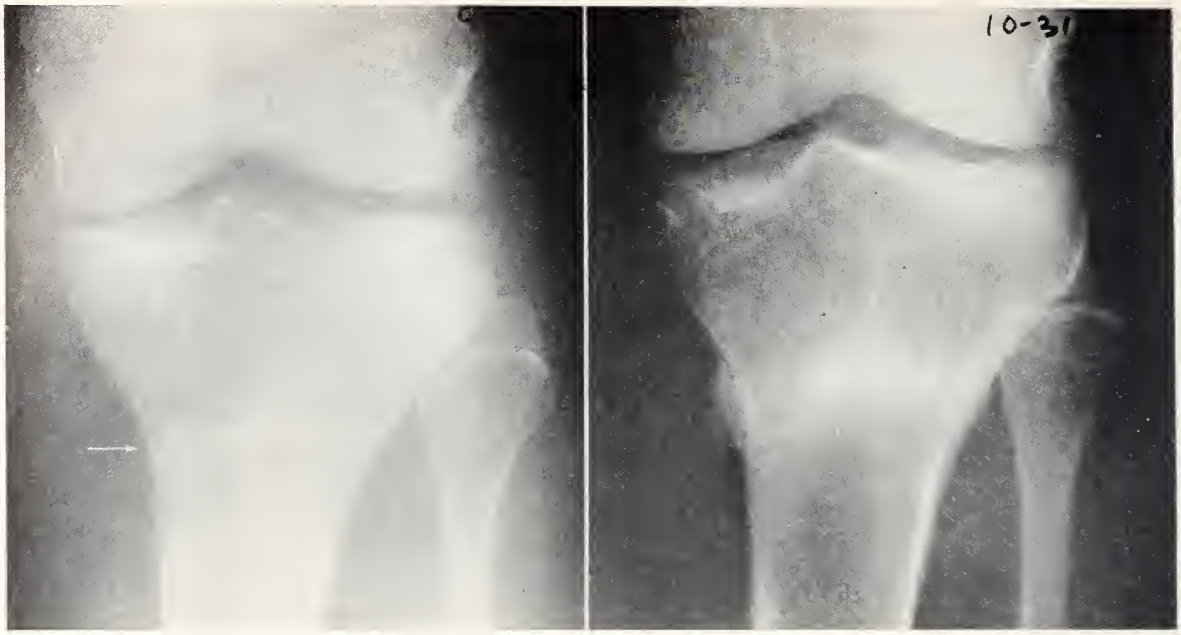


Figure 2.—Left knee of a 23-year-old recruit. At time of examination, pain had been present for two and one-half weeks. There was tenderness over the proximal tibia below the knee joint. At left is initial x-ray film and at right a film taken five weeks later when the patient was asymptomatic.

Whenever a possible diagnosis of fatigue fracture is encountered the quality of the bone may be questioned. Although the affected bone may have inert defects in crystalline structure, trabecular orientation or ground substance, we cannot detect, by the gross clinical methods of evaluation now available, any abnormality of bone affected by fatigue fracture.

Symptoms and Signs

The one constant symptom in this disorder is pain associated with physical stress of the part. Generally, there is associated swelling and tenderness over the involved part of the bone. Occasionally, ecchymosis or erythema may be seen. The pain and swelling usually subside with rest of the affected part. These symptoms and signs are, of course, most frequently encountered in persons undergoing basic military training, but they also occur in weekend sportsmen or in athletes performing at their maximum. These fractures, previously thought to be almost exclusively a military problem, are being recognized more and more frequently in civilian practice. Among the most important factors in accurate diagnosis are a history of pain associated with generally unaccustomed stress, an awareness by the physician of the possibility of the disorder and the availability of serial roentgenograms to confirm the suspicion.

Roentgenograms

Although the diagnosis of fatigue fractures may be tentatively established by an appropriate history combined with findings of localized pain, tenderness and edema over the affected bone, confirmation depends upon the progressive changes of the disorder as observed roentgenographically.

There are probably many fatigue reactions in bone which, owing to reduction of the initiating stress, do not reach a point at which signs are roentgenographically diagnostic. This possibility may explain the so-called "growing pains," "shin splints" and "ligamentous strains," which are poorly understood.

Early films are generally normal. Frequently, changes are not observed for 14 to 21 days or longer. Callus (either endosteal or periosteal) or a cortical crack may then be seen. The rate and degree of progression depends on the amount of continued stress and on the particular bone or area involved. In the metatarsal or fibula, a crack may be the first roentgenographic sign. In the tibial plateau, femur, or femoral neck, endosteal or periosteal callus may be the first sign observed on x-rays. Complete fracture, if it develops, generally occurs two to three weeks after the onset of symptoms. Figures 1 to 6 illustrate the development of these fractures in various bones.

It should be pointed out that, because of the length of time between the onset of symptoms and the development of findings that are visible on x-ray films, many cases of fatigue fracture are completely missed or misdiagnosed, especially in civilian practice (since the symptoms subside with decrease of activity, serial x-ray films are not obtained).

Differential Diagnosis

Occasionally the diagnosis of fatigue fracture may be quite difficult and, at times, must be established largely by exclusion. Several conditions may be confused with fatigue fracture and must be distinguished. These include:

- Pathologic fractures seen in congenital defects, general systemic disease and metastatic bone tumors;
- Pseudofractures, or "Umbauzonen," such as occur in Paget's disease, osteomalacia, rickets and Milkman's syndrome;
- Primary malignant disease of bone, such as osteogenic sarcoma, Ewing's tumor or reticulum cell sarcoma;
- Osteitis due to tuberculosis or syphilis;
- Simple fracture due to violence;
- Osteomyelitis.

Pathologic fractures and, especially, so-called pseudofractures are the cause of most of the problems in differential diagnosis.

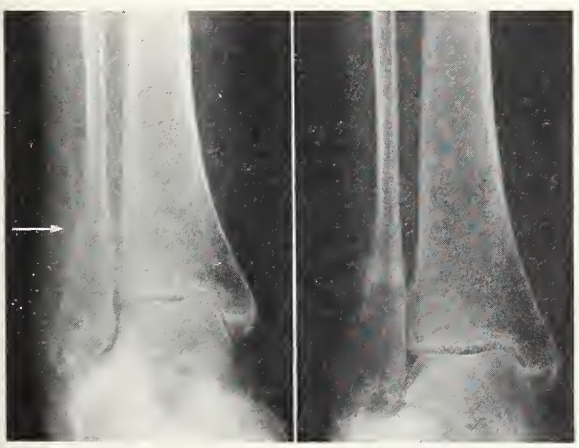


Figure 3.—Right ankle of a 68-year-old woman. Pain had been present for two and a half weeks and there was edema and tenderness over the distal fibula above the ankle joint. In initial x-ray film (left) fatigue fracture (arrow) is seen at upper border of syndesmosis. Treatment included a Gelocast wrapping and limited weight-bearing. Film taken five weeks later (right) shows progression of healing.

In general, pathologic fractures can be distinguished because they occur in obviously diseased bone affected by such disorders as tumor, leukemia, osteoporosis and metabolic bone disease.

Pseudofractures may be described as transverse zones of rarefaction varying in width from less than a millimeter to more than a centimeter, and usually symmetrical in distribution. In addition to their occurrence in rickets, osteomalacia and Milkman's syndrome, they have been described in association with renal rickets, coeliac disease, chronic idiopathic steatorrhea and Paget's disease. They are usually of two types. The first type is associated with malacic diseases and appears as small subperiosteal notches in the cortex when viewed tangentially, or as small, irregular, circular, punched-out zones of decalcification when viewed *en face*. This type slowly progresses across part or all of the bone as a band of decalcification. Periosteal reaction, sometimes observed in curved bones, may be apparent only on the concave side. The second type of pseudofracture is not associated with malacic disease and appears as cracks or fissures extending through the cortex on one side, most often on the convex surface of pathologically curved bones. Defects of this type are seen in Paget's disease.

These defects, or "pseudofractures," differ from actual fractures in several respects: They develop spontaneously without gross trauma and there is no crepitus or undue mobility except for a slight degree of "elastic give." The similarity of "pseudofracture" to fatigue fracture and the source of confusion in diagnosis are apparent. However, as now accepted, they are two entirely separate entities. The importance of accurate differentiation for purposes of treatment and prognosis is obvious.

Fatigue Fracture Following Immobilization. I have recently seen a type of fracture that I feel deserves mention because it might at some time also perplex others. This fracture is associated with increased activity or weight-bearing after a period of bed rest or immobilization. It has elements of both a true fatigue fracture and a pathologic fracture in that it is seen in bone which has become osteoporotic because of disuse.

Treatment

Early recognition of a fatigue fracture is of primary importance in treatment. This is especially true in the case of fractures of the femoral neck,

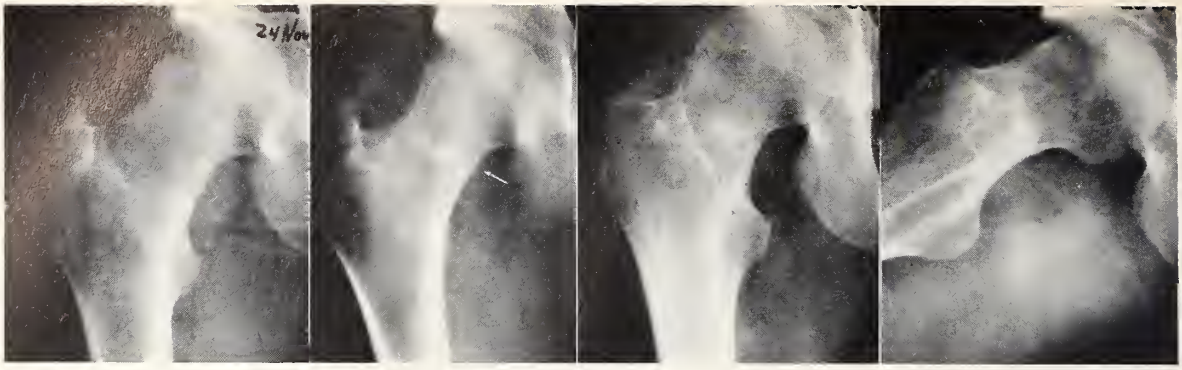


Figure 4.—Right hip of a 24-year-old recruit with a history of pain in the right hip which had lasted approximately ten days. Reading from left to right are: Initial x-ray film, interpreted as normal; tomogram of the hip three and a half weeks later, demonstrating fatigue fracture of the femoral neck (arrow) with endosteal and slight periosteal callus; anteroposterior and lateral views nine days later when the patient was asymptomatic.

where displacement may lead to serious or even disastrous consequences. Treatment for any bone in an early stage of the lesion may consist simply of curtailment of activity or rest of the part. When x-ray studies suggest that fracture may occur, or that a complete fracture already has occurred, immobilization in a cast is usually indicated. (Decision as to whether to apply a cast depends on the severity of the symptoms and the particular bone involved.) In the case of fractures of the femoral shaft and, particularly, the femoral neck, open reduction and internal fixation may be required.

Etiology

In the past, many theories regarding the cause of fatigue fractures have been advanced. These include: Nutritional deficiency; polyhypovitaminosis; local or systemic infection; vascular changes; pull of muscles and ligaments; and[5] "disproportion" between "required" and "inherent" capacity of the bone to bear stress. Most of these theories have been discarded, in part or in whole, in the light of more recent information.

Since the relationshp of fatigue, or stress, fracture to repeated minor stresses (rather than to one specific injury) has been recognized, frequent efforts have been made to equate this phenomenon to fatigue disruption in metal and other inert material. This correlation contributes somewhat to our understanding of etiologic factors, but the living, dynamic quality of the bone in which the fracture occurs must be emphasized. It is common knowledge that bone is remarkably sensitive to and indicative of the amount of stress or use to which it is subjected. That disuse or immobilization leads to osteoclastic resorption is well known. It is, perhaps, more surprising that overuse also leads initially to resorption of bone. Weinmann and Sicher[13]



Figure 5.—Right hip of a 24-year-old recruit who had had pain in the groin and thigh for two weeks. During marching, the right leg suddenly gave way. At left is initial x-ray film, anteroposterior view. Center panel, five days later, after Smith-Petersen nailing. Despite poor reduction, the fracture eventually healed. Film at right was taken six months after nailing. The nail was removed one year after insertion.



Figure 6.—Typical progression of a fatigue fracture of the ischiopubic ramus. X-ray films were taken one and a half weeks, three and a half weeks and eight weeks after onset of symptoms. Initial film appears normal; progressive formation of callus is seen in second and third.

said, "Increase of pressure or tension beyond the limits of tolerance leads to destruction of bone by resorption. . . ."

Johnson and coworkers[10] studied, with use of specimens taken for biopsy, the development of fatigue fracture of the tibia in 30 cases in which the duration of symptoms and roentgenographic signs ranged from seven days to seven months.

During the first week, localized pain, tenderness, swelling and erythema were associated with very active osteoclastic resorption of the cortex as shown by local osteoporosis. Before resorption began, lamellar birefringence in polarized light was reduced. The normal sharply structured lamellar pattern became smudged or lost in the area of fracture. There appeared to be an "unraveling" of marginal lamellar fibrils with consequent decrease in parallel orientation of the fibrils in the collagen bundles that constitute the lamellae. Resorption followed the partial disorganization of the collagen lamellar structure. During the second week, periosteal (occasionally endosteal) callus formation occurred. Resorption was complete at three weeks and callus formation was maximal at approximately six weeks.

Remodeling, or transformation, from circumferential lamellar bone to osteonal bone occurs between 18 and 28 years of age. All biopsy specimens showed development of the lesion within unosteonized lamellar bone. It appears, therefore, that fatigue fracture may represent an acceleration of the normal internal remodeling of circumferential lamellar bone to adult osteonized bone.

Knowledge of the mechanisms by which stress affects osteogenesis and the replacement, or turnover, of bone is, therefore, necessary before complete understanding of the causes of fatigue fractures is possible. Recent work by Bassett[2] on electrical effects in bone appears to suggest a link between mechanical stress and biological activity in bone. Because bone is so highly crystalline, bending forces on bone generate electricity, roughly in proportion to the amount of its deformation. This is due to a piezoelectrical effect produced by one or all of three mechanisms: (1) Stress or bending of collagen fibers; (2) bending of mucopolysaccharide molecules; (3) stress on collagen-hydroxyapatite interface (a semiconductor of the P-n type). Areas under compression (concave) are negatively charged, while convex areas are positively charged. Deposition of bone is influenced by weak, artificially induced currents and occurs in the area of electronegativity, or concavity. The converse, that is, that electropositivity causes osteoporosis of bone, has not been demonstrated.

Present etiologic knowledge of fatigue fractures can be summarized as follows. Fatigue fracture begins with excessive elastic deformation and recoil of bone, causing an "unraveling" of the lamellar structure of a segment of older circumferential

bone. Subsequent local resorption of the circumferential bone is followed by replacement with osteonal bone, a normal process accelerated by stress and, perhaps, mediated by electrical activity. If this acceleration is too rapid, resorption occurs more rapidly than replacement, causing local osteoporosis followed by callus formation. If mechanical stress is too great, complete fracture occurs.

REFERENCES

1. Aleman, O.: Tumors of foot from long marches (syndesmitis metatarsea), T. Milit. Hälsov., 54:191, 1929.

2. Bassett, C. A. L.: Electrical effects in bone, Sci. Amer., 213:18, Oct. 1965.

3. Blecher, A.: Uber den Einfluss des Parademarsches auf die Entstehung der Fussgeschwulst, Med. Klin., 1:305, 1905.

4. Blickenstaff, L. D., and Morris, J. M.: Fatigue fractures of the femoral neck, J. Bone Joint Surg., 48-A:1031, Sept. 1966.

5. Brandt, G.: Schleichende Frakturen (Umbauzonen, Uberlastungsschäden), Ergebn. Chir. Orthop., 33:1, 1941.

6. Breithaupt: Zur Pathologie des menschlichen Fusses, Med. Z., 24:169, 5 Sept. 1855; 24:175, 12 Sept. 1855.

7. Burrows, H. J.: Fatigue fractures of the fibula, J. Bone Joint Surg., 30-B:266, May 1948.

8. Burrows H. J.: Spontaneous fracture of the apparently normal fibula in its lowest third, Brit. J. Surg., 28: 82, July 1940.

9. Hullinger, C. W.: Insufficiency fracture of the calcaneus: Similar to march fracture of the metatarsal, J. Bone Joint Surg., 26:751, Oct. 1944.

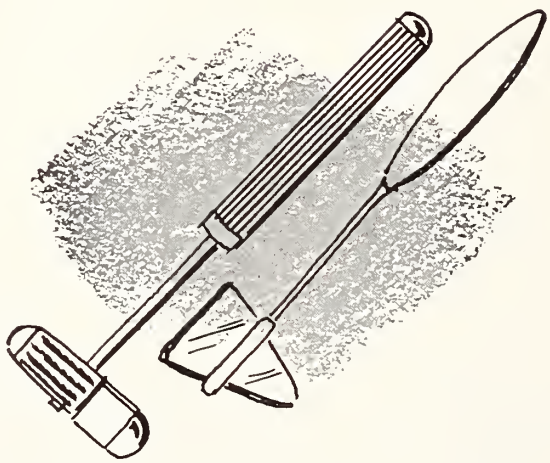
10. Johnson, L. C., Stradford, H. T., Geis, R. W., Dineen, J. R., and Kerley, E. R.: Histogenesis of stress fractures. Armed Forces Institute of Pathology Annual Lectures, 1963. (Abstract in J. Bone Joint Surg., 45-A: 1452, 1963.)

11. Pauzat, J. E.: De la périostite ostéoplasique des métatarsiens à la suite des marches, Arch. Méd. Pharm. Mil., 10:337, 1887.

12. Stechow: Fussoedem und Röntgenstrahlen, Deutsch. Mil.-ärztl. Z., 26:465, 1897.

13. Weinmann, J. P., and Sicher, H.: Bones and Bones: Fundamentals of Bone Biology, 2nd ed., C. V. Mosby Co., St. Louis, 1955, p. 138.

14. Weisbach: Die sogenannte "Fussgeschwulst," Syndesmitis metatarsea, der Infanteristen in Folge von anstrengenden Märschen, Deutsch. Mil.-ärztl. Z., 6:551, 1887.



On Sexual Apathy in the Male

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■ *Ever since World War II, there has been a noticeable change in the sexual behavior and responses in men and women. Women, in general, are becoming sexually more assertive and demanding and men more indifferent and lethargic. In patients of middle age, sexual boredom is particularly pronounced in men, whereas the post-menopausal female becomes more interested in sexual pleasure.*

In the youth of the "cool" generation, both boys and girls are quite open about sex, but their sexual activities precede emotional involvement. The similarities in dress and behavior of both sexes indicate a wish for a twin rather than a search for a lover. In the age group between 25 and 45, women demand equal orgasms since they have become economically independent and are relatively free of the fear of pregnancy. This seems to have mobilized a deep-seated unconscious fear and hatred of women in the male, making him sexually apathetic. In both sexes there is a growing alienation between romantic love and sex.

THIS PRESENTATION was prompted by clinical findings in the private practice of psychiatry and psychoanalysis that indicate men and women have changed in their sexual behavior and responses in the last 25 years. It is my definite impression that, in general, women are becoming sexually more assertive and demanding, and men are more indifferent and lethargic. Before World War II, the term "frigidity" was used exclusively in regard to women. Today I find far more men who display sexual coldness or disinterest. This is not only true for the chronologically mature and the middle-aged but it appears to be equally valid for the youth of this "cool" generation. There are other changes in sexual behavior, but I shall limit this communication to a description of some typical forms of sexual apathy and will attempt to explain some of the underlying causes.

I do not claim that my findings are statistically valid, but I have confirmed my own observations with many colleagues who practice psychoanalysis or psychiatry or who have made pertinent observations as gynecologists, urologists and general practitioners.

I propose to use the term *sexual apathy* to refer to behavior which indicates a conscious indifference, disinterest, unconcern and coldness toward sexual intercourse. I underline the fact that this is a conscious phenomenon because it is a well known fact that people may react and behave as if they had no sexual appetite but on closer scrutiny will be found to have hidden and distorted manifestations of libido. I prefer the term *apathy* to *frigidity* because it is broader in scope and avoids the femi-

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nine connotation associated with frigidity in the past.

Clinical Varieties of Sexual Apathy

The different categories I have selected for discussion are neither precise nor systematic. I chose to emphasize certain easily recognizable large groups.

Sexual Boredom in Middle Age

Men and women of 45 to 55 years of age and married some 20 to 25 years tend to find sex boring and uninteresting, a chore and an obligation. It is not rare to find men who use sexual intercourse with their wives primarily as a means of getting rid of unpleasant sexual tension, a guilt-free form of masturbation. In the past, women who had given up any hope of sexual pleasure would submit to this procedure passively in order to "relieve" the husband.

Today I find the situation changed, at least in the middle and upper economic and educational classes. The middle-aged woman of today, who has experienced sexual satisfaction in the early years of marriage, expects—in fact, it would be more precise to say, *demands*—sexual gratification. Even in the past, the middle-aged woman was far less apathetic about sex than the middle-aged man, a point which has been confirmed by the works of Kinsey,[4,5] Masters and Johnson.[6]

It would seem that the freedom from the fear of pregnancy, which the menopause brings, adds to the middle-aged woman's sexual assertiveness. There are other factors involved in this change, some of which I shall discuss later. At this point, I wish to focus on the sexual apathy of the middle-aged man.

There are many factors which contribute to the male's disinclination toward sex in middle-age. After 25 years of marriage, his sexual practices (in marriage) tend to become stereotyped and routinized. There are no more surprises or improvisations. Actually, he has stopped allowing himself to fantasy or to act upon his imaginings in the sexual situation. At age 45, the male has more or less achieved his full professional and economic status. If he is successful, he is concerned about maintaining his masculine "image." If he is a failure, he is loath to reveal any further defects in his virility. As a consequence of his insecurity about his masculinity, the middle-aged American male is inhibited in giving full rein to his sexual fantasies, because libidinal fantasies in general tend to have an infantile cast. A rich sexual life depends on one's freedom to enact with another person the different sensual longings which arise spontaneously in the sexual situation. The sexually healthy male and female enjoy one another's sexual infantilisms in the foreplay of the sexual act. Frightened people become inhibited and try to play it safe by following a set pattern. The resultant rigidities and routines make for sex without passion, which is boring.

Another complicating circumstance is the typical middle-aged man's notion that at his time of life his body has to be preserved from any undue stress and strain. He may play 36 holes of golf at his country club and cards afterwards, but at night, in bed with his wife, he is apt to feel sex is too strenuous and depleting. It is not rare to find men who act in bed as though the sexual act is a dangerous obligation they contracted for when they were young and foolhardy. They are more interested in preserving their body than their marriage. Sexual relations have become for them merely a biological need, a gonadal exercise, and no longer an intimate emotional experience. They want sex to be performed as a service, with little active participation on their part.

One of the typical clinical manifestations of sexual frustration in middle-age is the prevalence of somatic dysfunctions on a psychological basis.

Ever since Freud,[2] we have become increasingly aware of the human propensity to become fixated to, or to regress to, earlier forerunners of the drive for sexual intercourse. I am sure all physicians are familiar with the man who is a passionate collector of various possessions and who is correspondingly disinterested in sex. The obese patient has obviously sexualized eating and de-sexualized love-making. The drinker has substituted the quest for the drunken stupor in place of orgasm. The swallowers of tranquilizers have replaced the dull haze and partial oblivion of the drug for the fantasy life required by a good sex life. In all these patients there is a regression in the direction of anality, orality and narcissism and a turning away from human relations, love and sex.

In this group one should include those patients who have displaced their conflicts about sex into somatic channels and who develop physical problems on a psychological basis. The specific organ system afflicted often reveals the psychological fix-

ation point. Thus, disorders of the stomach and small intestine point in the direction of oral fixations, while illnesses of the lower bowel may indicate anal regression. All these patients are more or less apathetic about sex and use their somatic symptoms as a rationalization for avoiding sexual relations as well as a hidden substitute satisfaction. It is important for the physician to recognize that "prescribing" sexual intercourse will not correct these disorders. Also, careful medical evaluation is important in each case. The finding of pathological psycho-dynamics does not rule out other etiological factors.

The Sexuality of the "Cool" Generation

I believe it is important to interpolate at this point that the designation "cool" generation does not apply with equal validity to all the youth. I find it helpful to distinguish the cool "cools" from the warm "cools." The cool "cools" are best exemplified by the "beatniks," the removed, isolated and withdrawn individuals who refuse to become involved and committed to anything or anyone which has its roots in the past. Home, family, country, tradition, convention and ideals are all abhorred. They do relate to their fellow cools, but even then it is limited to the group as a whole and individual relations are marginal and tangential.

The warm "cools" also have a rebellious attitude toward most values of the past but they do become passionately involved in causes. They have been called "Vietniks" to distinguish them from the beatniks. They protest vociferously against the war in Viet Nam, they are intensely involved in the civil rights movement, they march in Selma, riot against the police on the Berkeley campus. The warm "cools" do become emotionally involved with individuals as well as groups, and although they do bear some similarity to the cool "cools," they also resemble the youth of the time before World War II.

It is a striking fact that most of the youth today are much more open about their sexual practices than they used to be. Teen-agers in the middle and upper classes think nothing of displaying quite intimate forms of necking and petting in the presence of their parents, something which was unheard of 30 years ago. It is worth noting that the young parents of this generation are willing, if not eager, to watch. In both boys and girls, sexual intimacy often precedes romantic love.[9] They get to know each other sexually before they become close emotionally or intellectually. This development is more pronounced in girls because in the past it was the female who required the feeling of being loved before she was able to respond sexually. In the past, it was the unpopular girl who used her sexuality for bait as a means of competing with the more attractive rivals. Today, even the most attractive and popular girls indulge in a variety of sexual practices with little emotional involvement.

This public sexuality does not lead to real sexual satisfaction, but on the contrary, indicates some degree of orgastic impotence. Quick and easy bodily intimacy and familiarity makes for promiscuity and "organ pleasures," but not for a rich sensual experience. A confirmation of this hypothesis, I believe, is to be found in the frequent use of LSD and marijuana by the youth. They use drugs in a vain attempt to bring color to their relatively colorless lives. The drabness stems from the emotional thinness of their interpersonal relations.

There seem to be several etiological factors responsible for these developments. On the one hand, the parents of the cool generation want their children to be popular, to be "in"; and the parents, too, want to be popular with the younger generation. Modern parents dread to say no to their offspring. They feel every deprivation might be a trauma—a word they use without real understanding. They also cannot bear to arouse the youngsters' anger. They want peace of mind, even if it causes peace-of-mindlessness. Clinical experience has demonstrated that people who cannot cope with the different varieties of hate, anger and resentment, will also have trouble with the different forms of love.

Insecure parents often need to alleviate their own anxiety by using the social success of their children. Young parents of today often push their children to "date" prematurely and, as a consequence, the youngster is emotionally unprepared for this experience. I believe one of the reasons the young males and females of today wear their hair alike and dress alike stems from their fear of the opposite sex. The boy and girl of today seek a twin, not a sweetheart or a lover. They are only secure with someone who resembles themselves. It is natural for the young to fear the opposite sex, but it becomes more pronounced when they are pushed into dating prematurely by their parents. The twinship in our present day youth is an attempt to com-

pensate for lack of a close friendship with someone of the same sex, an occurrence which their parents mistrust and oppose. (There is an increased dread of homosexuality in young parents). The twinship means sameness, familiarity and security. Once some degree of safety is established, sex becomes possible but it is low key and relatively unsatisfying.

The opposite sex is unfamiliar and strange, and therefore frightening. However, sexual differences also make for excitement and fascination. This is most clearly to be seen in the attitudes toward the genitals of the opposite sex, where the differences are most pronounced. If fear predominates, the sexual organs are felt to be repulsive or threatening. If the anxiety is overcome, the genitals of the opposite sex are perceived as tantalizing and attractive. One can observe a broad spectrum of reactions, from disgust and horror to captivation and rapture. This varies from person to person, and also within the same person, depending on his emotional state at a given time.

Another contributory factor to this clinical syndrome of impoverished sexuality is a past history of a life with a relative absence of frustration and the prevalence of quick and easy satisfactions. The height of sensual pleasure is achieved when sex is interwoven with romantic love. The full flowering of romantic love and passion requires a background of dealing with obstacles, suffering and frustration. The anthropologists, especially Margaret Mead,[7] have demonstrated this convincingly. The great lovers in real life and in literature were willing to endure great misery and pain for their loved ones. They were willing to wait, to struggle and to endure, all of which went to make the loved person more precious. The "cool" set is accustomed to quick and easy gratifications. Instant warmth and instant sex make for puny love, cool sex, and a turning to LSD and "pot."

Sexual Reactions in Adults

If we turn to adults between 25 and 45 years of age, we now seem to find an increase of sexual apathy in the male and sexual demandingness in the female. In both sexes there is a mounting tendency to divorce sexual relations from emotional involvement. This is particularly pronounced in the male. There are many men who can be libidinously very ardent and vigorous as long as it does not imply emotional commitment. A young woman patient of mine reported to me that she has been dating a 35-year-old man for several months. Each time he sees her he takes her out to dinner to an expensive restaurant, then to a fashionable nightclub or theatre and then wants to go to bed. During the course of the evening, however, the young man only speaks pleasant trivia or broad cliches. When my patient pointed out his evasiveness, he did not deny it. He replied that he liked her, he was quite eager to dine with her, dance with her and go to bed with her, but he didn't want to get "involved." It was not only his fear of marriage with the ensuing responsibilities; his behavior, I later learned, was based on the alienation of sex from love.

There are many patients who do not display a generalized sexual apathy but who are apathetic toward one type of love object. I refer here to people who are only able to feel passionate about someone strange or forbidden, and feel lethargic toward someone familiar and permissible. This is a very widespread phenomenon in our society, as our high divorce rate and flagrant marital promiscuity indicate. Every physician has seen patients who are sexually apathetic to their marital partner yet are carrying on a torrid love affair outside the marriage. If you explore this matter you will find that the person involved is unable to feel passion to the person he is married to. It is quite typical to get a history that before marriage, and even in the early years, there was a great deal of sexual desire which slowly petered out. I should note at this point that, in the past, this situation was predominant in the male. Now it is equally true of the female.

The underlying psychopathology in such cases seems to be based on several crucial elements. In the first place, people in this category were never able to overcome that taboo of childhood, when it was forbidden to have sexual impulses toward members of the family. Unconsciously, the people one lives with become familiar—that is, family—and therefore desexualized.

Another important factor is the increase in hostility and fear between the sexes, above all in men, which seems to have mounted with the increasing ascendency of women.[1] As women in our society have become more assertive and daring, men seem to have become more passive and timid, in life in general, and particularly in sexual matters. As women have gained greater freedom economically

and politically, and are less afraid of pregnancy, due to the "pill" and other modern contraceptive devices, they are able to achieve orgasm far more readily than they did in the past. Today, women tend to feel entitled to equal orgasms along with their other equal rights. In the past, a woman needed the feeling of being loved as a prerequisite for sexual gratification. Now she seems just as able as men to enjoy fornication without romantic love. The separation and estrangement of love from sex is an extremely important source of today's sexual problems, and although it is a complicated topic, I want to sketch briefly some of the underlying psychological causes.

As I observe some of the most obvious clinical signs, I conclude that women are far more certain of their femininity than men are of their masculinity. For example, a woman is at her most feminine in the company of men. Many men in our society feel most manly at a "stag" party or poker game—that is, in the company of men. In the past, we would have explained this on the basis of the male's fear of the castrating, penis-envying woman. Although there is some validity to this concept, I believe today we would be more inclined to recognize the fact that one's gender identity, one's sense of belonging to a given sex and not another, stems from very early childhood experiences that long pre-date the phallic phase.[3,8] In early childhood the child tends to identify as he perceives and learns. Since children are reared by mothers, both boys and girls will identify with the mother. Girls learn to become feminine by their contact with mother. The boy has to switch his identification and has to have meaningful contact with a masculine father to become manly. This is harder to obtain in our society because fathers spend far less time with the young child and have increasing difficulty in asserting their maleness.

Furthermore, the mother is by far the source of the greatest pleasure and security in early childhood of both boys and girls. It is an all too human tendency to envy, to want to possess for oneself, that which is so valuable. We have long recognized the female's envy of the male in our society. But we have neglected the much deeper and older envy of mother, particularly in men. On the surface, men have contempt for women. But below the surface is a repressed envy. This is true for all inappropriate contempt—it covers hidden envy. I believe the deep seated *unconscious* hatred and fear of women is the underlying basis for the sexual apathy in the male. The original source of this hatred is the male child's dependency on the omnipotent-appearing mother. As long as women were timid and demure about sex, men were able to assume a dominating and aggressive role. Now that women have become sexually more aggressive and outspoken, it seems that the latent fear became mobilized and manifests itself in the male's avoidance of sex.

There are many other factors which should be mentioned, even if I cannot discuss them. The welfare state tends to act like a mother, taking care of the sick, the poor, the unemployed and the aged. This tends to feminize men and to blur the distinction between males and females. This is particularly true in all collectivist states and in people living on the dole. I believe this is observable in the Soviet Union, in the Kibbutz in Israel, and in armies which use women. Finally, the emphasis on security as the goal of life makes for the quest for peace-of-mindlessness, early retirement and a general emotional uninvolvement. Loving is risk-taking. It implies daring to be vulnerable and hurt. In this sense, the search for security is the enemy of loving and in our society the emphasis is on security. One of the results of this attitude is the splitting off of love from sex, and consequently we so frequently find love without passion and sex without emotional involvement.

REFERENCES

1. Borgese, E.: Ascent of Woman, George Braziller, New York, 1963.

2. Freud, S.: Three Essays on the Theory of Sexuality, Standard Edition, 7:125, London, 1962.

3. Greenson, R.: On homosexuality and gender identity, Int. J. Psychoanal., 45:217-219, 1964.

4. Kinsey, A., Pomeroy, W., and Martin, C.: Sexual Behavior in the Human Female, W. B. Saunders Co., Philadelphia, 1948.

5. Kinsey, A., Pomeroy, W., Martin, C., and Gebhard, P.: Sexual Behavior in the Human Female, W. B. Saunders Co., Philadelphia, 1953.

6. Masters, W., and Johnson, V.: Human Sexual Response, Little, Brown & Company, Boston, 1966.

7. Mead, M.: Male and Female, William Morrow & Co., New York, 1949.

8. Stoller, R.: A contribution to the study of gender identity, Int. J. Psychoanal., 45:220, 1964.

9. Wolfenstein, M.: Changing Patterns of Adolescence, Ciba-Symp., pp. 195-208, J & A Churchill, Ltd., London, 1965.

Hereditary Hemolytic Anemias Associated with Specific Erythrocyte Enzymopathies

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IT IS INCREASINGLY apparent that the hereditary hemolytic anemias of man comprise a vast and variegated spectrum of diseases, some comparatively common and some very rare, which have genetically determined aberrations in either structural or catalytic (enzyme) proteins of the erythrocyte. In some, the inborn error results in the presence of an abnormal hemoglobin; in some, such as the thalassemic syndromes, inability to synthesize adequately one or another component of globin appears to be the fundamental abnormality; in some, such as those forming the subject of this review, specific enzyme deficiencies constitute the molecular basis of anemia. In still other instances, including hereditary spherocytosis, the precise etiology at the molecular level remains undefined.

Normal Erythrocyte Metabolism

The mature human erythrocyte has lost much of the metabolic machinery characteristic of the other nucleated cells of the body. It has no nucleus, no ribosomes, mitochondria or other intracellular organelles, only ineffectual vestiges of Kreb cycle metabolism, and no capacity for oxidative phosphorylation. Beyond the reticulocyte stage, it retains no mechanism for synthesizing new protein. Some 95 percent of its dried weight is hemoglobin, which performs its crucial metabolic functions without expenditure of energy. However, its simple metabolic requirements are so geared to its restricted capabilities that it normally survives 120 days and more than 100 miles of travel in the circulation. Nonetheless, its energy requirements, while small, are still finite. It must maintain its biconcave, discoidal shape, pump sodium out of and potassium into its intracellular environment against electrochemical gradients, protect itself from oxidative stresses in its surroundings, and prevent significant conversion of its oxyhemoglobin to methemoglobin. Under normal conditions, there is slow denaturation of its crucial metabolic proteins each of which, under any given set of circumstances, has its individual biological half-life. Presumably its ultimate destruction results from attrition of its metabolic capacities and its eventual inability to provide even the austere energy requirements necessary for survival.[1-5]

The mature erythrocyte in man derives essentially all of its energy requirements from the conversion of glucose to lactate. Chart 1 indicates the available routes of glucose metabolism. Glucose, phosphorylated by hexokinase to glucose-6-phosphate (G-6-P), may traverse two main pathways. The quantitatively predominant Embden-Meyerhof pathway results in the anaerobic production of two moles of lactate for each mole of glucose metabolized. In the first half of the cycle, triose is formed from glucose, and energy is expended in the form of the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) at the hexokinase and phosphofructokinase mediated steps.

In the simplest illustration, this initial energy loss is more than compensated by the production of four moles of ATP from one mole of glucose (two of triose) traversing the terminal half of the pathway. Two moles of ATP are regenerated from ADP at the phosphoglycerate kinase step, and two more at the point of the pyruvate kinase mediated reac-

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tion. The net result is a gain of two moles of high energy ATP from each mole of anaerobically metabolized glucose. This net gain, however, may be materially reduced if triose by-passes the ATP generating phosphoglyceratekinase reaction by traversing the energy wasteful Rapaport-Luebering shunt[6,7] shown in Chart 1. The latter is a unique feature of the erythrocytes of man and certain, but not all, mammalian species. The glycolytic intermediate, 1,3-diphosphoglycerate (1,3-DPG) may

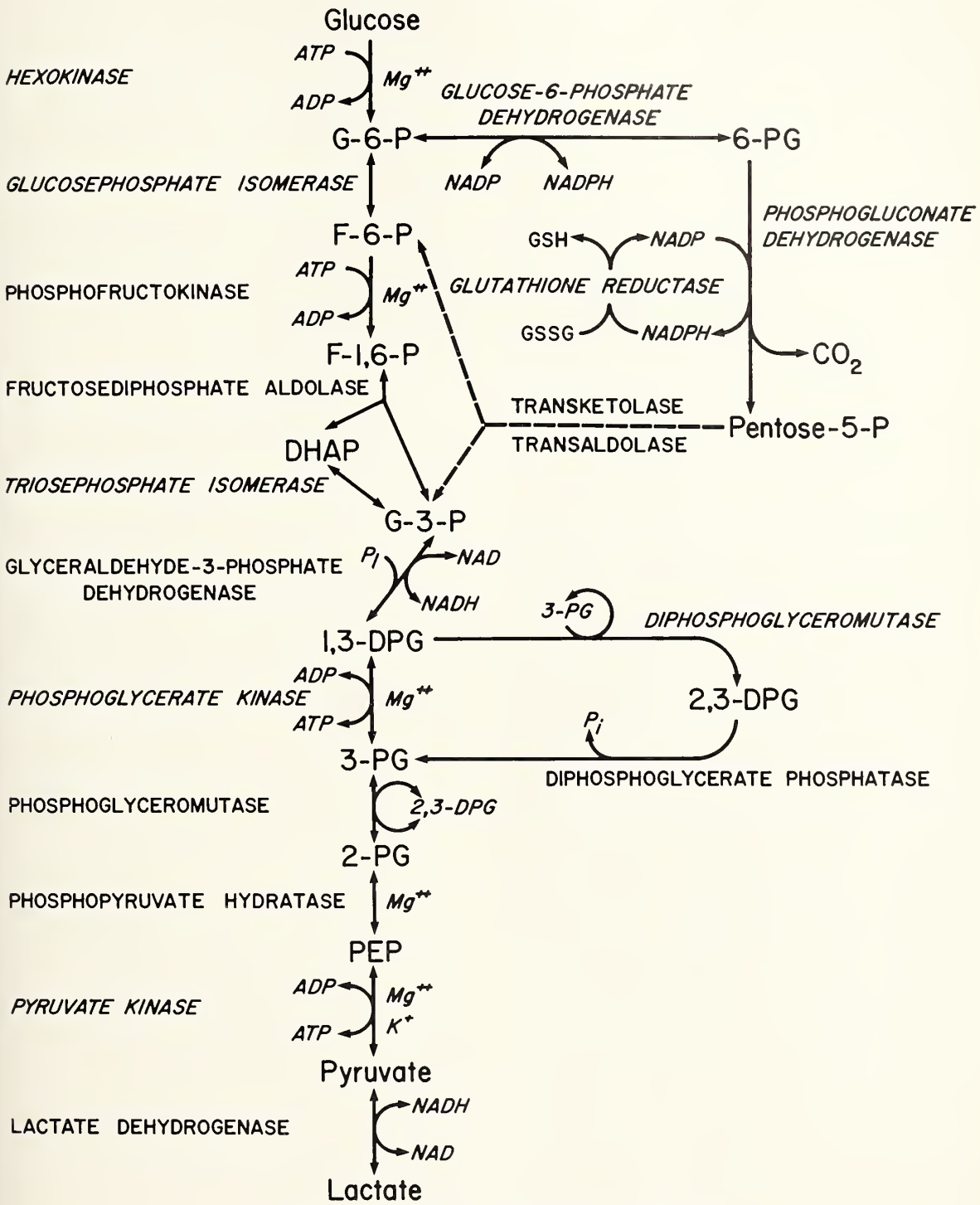


Chart 1.—The pathways of erythrocyte glycolysis.

be mutated enzymatically to 2,3-diphosphoglycerate (2,3-DPG), and the latter may accumulate to the point where at times it contains some 50 percent of the total erythrocyte organic phosphorus.[8] It, in turn, may be dephosphorylated and returned to the mainstream of glycolysis as 3-phosphoglycerate (3-PG), which is also the product of the alternative phosphoglycerate, kinase reaction of the anaerobic pathway.

It is apparent that if glucose were entirely metabolized via 2,3-DPG—that is, through the Rapaport-Luebering shunt—two moles of ATP would be lost before the formation of triose, and only two moles would be later generated (at the pyruvate kinase step only). No net gain would result from this exercise in futility. Therefore, in considering the strictly anaerobic erythrocyte metabolism of a mole of glucose, a net gain of somewhere between 0 and 2 moles of ATP will result, depending on what proportion of glucose passes through the 2,3-DPG pool. The latter may be important in regulating intracellular ATP/ADP ratios and level of inorganic phosphorus, and may also serve as a reservoir of substrate when glucose is temporarily depleted in the environment of the cell. In the anaerobic cycle, the pyridine co-factor is diphosphopyridine nucleotide (NAD) and this is cyclically reduced at the triosephosphate dehydrogenase step to NADH and reoxidized in the course of the terminal lactate dehydrogenase reaction.

While normally some 90 percent of glucose is thought to traverse the anaerobic route,[9] a significant and highly variable portion of glucose is metabolized via the so-called hexose monophosphate (HMP) oxidative shunt, likewise shown in Chart 1. Glucose-6-phosphate oxidized by this alternative pathway is converted to pentose through the action of two dehydrogenases. Pentose so generated is, through a series of enzymatically catalyzed reactions, again converted to fructose-6-phosphate (F-6-P) and glyceraldehyde-3-P (G-3-P), intermediates of the Embden-Meyerhof pathway which ultimately become lactate. It should be noted that triphosphopyridine nucleotide (NADP) is the co-factor operative in the oxidative shunt. It is reduced to NADPH by the first two dehydrogenase reactions, during which CO_2 is evolved and pentose formed. NADPH is reoxidized by enzymatic reactions outside of the strictly glycolytic metabolism. The most important of these, catalyzed by NADPH-linked glutathione reductase, maintains glutathione (GSH) in its reduced form. NADP regenerated in this manner is again available to participate in the metabolism of the HMP oxidative shunt.

While quantitatively less active than the anaerobic cycle under normal conditions, the HMP shunt is greatly stimulated by oxidative stresses resulting in glutathione oxidation, and NADPH, generated by the shunt here permits the important glutathione reductase reaction to proceed. This constitutes a protective mechanism invoked, for example, in the face of the challenge of oxidative damage resulting from the administration of certain drugs. Under such conditions, the operation of the HMP shunt may be crucial to cell survival. In view of the highly restricted metabolic resources of the erythrocyte, it is not surprising that a variety of highly specific and sharply localized inborn metabolic errors should result in impaired survival and, hence, in hemolytic anemia.

Hemolytic Anemia and Erythrocyte Enzyme Deficiency

The ultimate definition of the molecular etiology of the now recognized enzyme deficiency associated hemolytic anemias received major impetus from two main sources. The first of these resulted from a revival of interest in the known induction of severe hemolytic episodes in a significant proportion of persons receiving antimalarial agents such as primaquine.[10] Extensive studies during and after World War II culminated in 1956[11] in the recognition that "primaquine sensitivity" was conditioned by a specific deficiency of glucose-6-phosphate dehydrogenase (G-6-PD), the first enzyme of the HMP shunt pathway. For the first time the mechanism of an adverse reaction to a drug, whose administration was benign in most but catastrophic in a few, was defined at the molecular level and shown not to be on an immunological basis.

The second impetus derived from the studies of Dacie and his colleagues[12] in England. These workers were interested in certain relatively uncommon hemolytic anemias which they characterized as "nonspherocytic," in contrast to the better known disorder of hereditary spherocytosis. This heterogeneous group of hereditary anemias possessed certain clinical and laboratory features in common. No hemoglobinopathy was demonstrable, the antiglobulin (Coombs) test was negative, the osmotic fragility of fresh cells was usually normal, splenomegaly was the rule, and splenectomy (unlike the situation in hereditary spherocytosis) at best ameliorated, but did not clinically correct,

the disorder. Studies of glucose metabolism in the reticulocyte-rich, young erythrocyte populations of affected subjects in some instances suggested relatively deficient glycolysis and raised the question of some form of metabolic impairment in sugar utilization.

Selwyn and Dacie[13] devised an *in vitro* "autohemolysis" test whereby sterile, defibrinated blood, with and without additives such as glucose, was incubated at 37°C for 48 hours and spontaneous hemolysis was quantitated. Different patterns were observed among the cell populations from different subjects studied. In one, categorized as Type I, autohemolysis was only slightly greater than in normal blood, and was nearly, but not quite, correctible by adding glucose during the incubation. In a second, Type II, autohemolysis was usually severe, and was poorly if at all corrected by additives of glucose or adenosine. The test, although since shown to lack critical specificity, suggested the heterogeneity of these hereditary disorders. A little later de Gruchy and his colleagues[14-16] in Australia measured glycolytic intermediate levels in the erythrocytes of similar cases. In certain instances an abnormal accumulation of intermediates suggested "pile-up" behind a point of metabolic block, which appeared to be distal to triose formation. Again, a defect in the glycolytic machinery was suggested. In 1961 the first of several genetically determined erythrocyte glycolytic enzyme deficiencies associated with chronic hemolysis—that of pyruvate kinase deficiency—was defined by Valentine, Tanaka and Miwa.[17,18]

Classification (Table 1)

At present a number of hemolytic anemias in which the inborn error has been identified are recognized. These enzymopathies may be categorized as follows:

(1) Enzymatic deficiencies in the oxidative HMP shunt pathway. G-6-PD deficiency has been widely studied.[10,19] A few reports[20,21] of possible association of hereditary hemolytic anemia with partial 6 phosphogluconate dehydrogenase (6-PGD) deficiency are available, but a cause-effect relationship here is uncertain.

(2) Enzymatic deficiencies in non-glycolytic enzymes. Chronic hemolytic anemia associated with erythrocyte glutathione reductase (GSSG-R) deficiency has been observed by Löhr and Waller.[22] Carson and co-workers[23] have reported a milder deficiency of the same enzyme associated with susceptibility to primaquine hemolysis but not with chronic anemia. Harvald and his associates[24] have reported hereditary hemolytic anemia in two young men with a deficiency of adenosine triphosphatase (ATPase). This was regarded as a probable cause of the anemia. Necheles and coworkers[25] have recently described a relatively severe deficiency of the enzyme glutathione peroxidase in a male subject who exhibited a hemolytic reaction after transfusion, and a probable mild, compensated hemolytic disorder after recovery. Glutathione peroxidase catalyzes the oxidation of glutathione by peroxides, and evidence suggests it is of importance in protecting cellular proteins from peroxidative denaturation. Oort, Loos and Prins and their colleagues[26-28] have extensively studied a kindred in which certain members have a moderately severe hemolytic process and nearly complete absence of erythrocyte glutathione. The inborn error is thought to be inability to fully synthesize the tripeptide glutathione.

(3) Deficiencies in enzymes of the anaerobic glycolytic pathway. Hemolytic disorders associated with inherited deficiencies of the enzymes pyruvate kinase (PK),[17,18,19,29,30] triosephosphate isomerase (TPI),[31-33] hexokinase (HK),[34,35] glucosephosphate isomerase (GPI),[36,37] phosphoglycerate kinase (PGK),[38a-b] and of 2, 3-diphosphoglyceromutase (2, 3-DPGM)[39-42] are now established.

HMP Oxidative Shunt Pathway Enzyme Deficiencies

G-6-PD Deficiency

The fact that the antimalarial agent pamaquine is capable of causing hemolytic episodes in certain persons had been known since 1926.[43] In 1948 Earle and associates[44] noted that about 10 percent of American Negroes were susceptible, while hemolysis was relatively rare in Caucasians in this study. Similar findings were reported for primaquine by Hockwald and co-workers[45] in 1952, and in 1954 Dern and co-workers[46] clearly demonstrated an intrinsic erythrocyte abnormality in susceptible subjects. Chromium-labeled erythrocytes from patients with "primaquine sensitivity" were rapidly destroyed after transfusion into normal persons when primaquine was given to the recipient. Conversely, normal erythrocytes, isotopically labeled and transfused into primaquine-sensitive subjects, exhibited unimpaired survival when the drug was subsequently administered.

TABLE 1.—*Erythrocyte Enzymopathies Associated with Hereditary Hemolytic Anemia*

Deficient Enzyme	*Reaction Catalyzed*
A. *HEXOSEMONOPHOSPHATE-SHUNT ENZYME DEFICIENCIES*	
1. Glucose-6-phosphate dehydrogenase:	$\text{G-6-P} + \text{NADP} \overset{\text{G-6-PD}}{\longleftrightarrow} \text{6-PG} + \text{NADPH}$
2. 6-Phosphogluconate dehydrogenase:	$\text{6-PG} + \text{NADP} \overset{\text{6-PGD}}{\longrightarrow} \text{Ru-5-P} + \text{CO}_2 + \text{NADPH}$
B. *NONGLYCOLYTIC-ENZYME DEFICIENCIES*	
1. Glutathione reductase:	$\text{GSSG} + 2\ \text{NADPH} \overset{\text{GSSG-R}}{\longleftrightarrow} 2\ \text{GSH} + 2\ \text{NADP}$
2. Adenosine triphosphatase:	$\text{ATP} \xrightarrow[\text{Na}^+\ \text{K}^+\ \text{Mg}^{++}]{\text{ATP-ase}} \text{ADP} + \text{P}_i$
3. Glutathione peroxidase:	$2\ \text{GSH} + \text{H}_2\text{O}_2 \overset{\text{GSH-Px}}{\longrightarrow} \text{GSSG} + 2\ \text{H}_2\text{O}$
4. Glutathione synthetase:	(a) $\text{Glu} + \text{Cyst} \xrightarrow[\text{ATP}\ \text{Mg}^{++}]{\text{GS-I}} \gamma\text{-Glutamyl Cyst} + 2\ \text{ADP} + 2\ \text{P}_i$
	(b) $\gamma\text{-Glutamyl Cyst} + \text{Gly} \xrightarrow[\text{ATP}\ \text{Mg}^{++}]{\text{GS-II}} \text{GSH}$
C. *GLYCOLYTIC-ENZYME DEFICIENCIES*	
1. Pyruvate kinase:	$\text{PEP} + \text{ADP} \overset{\text{PK}}{\underset{\text{K}^+\ \text{Mg}^{++}}{\longleftrightarrow}} \text{Pyruvate} + \text{ATP}$
2. Triosephosphate isomerase:	$\text{DHAP} \overset{\text{TPI}}{\longleftrightarrow} \text{G-3-P}$
3. Hexokinase:	$\text{Glucose} + \text{ATP} \xrightarrow[\text{Mg}^{++}]{\text{HK}} \text{G-6-P} + \text{ADP}$
4. Glucosephosphate isomerase:	$\text{G-6-P} \overset{\text{GPI}}{\longleftrightarrow} \text{F-6-P}$
5. Phosphoglycerate kinase:	$\text{1,3-DPG} + \text{ADP} \overset{\text{PGK}}{\underset{\text{Mg}^{++}}{\longleftrightarrow}} \text{3-PG} + \text{ATP}$
6. Diphosphoglyceromutase:	$\text{1,3-DPG} \xrightarrow[\text{3-PG}]{\text{DPGM}} \text{2,3-DPG}$

Abbreviations: G-6-P = glucose-6-phosphate, 6-PG = 6-phospho-3-keto gluconate, Ru-5-P = ribulose-5-phosphate, PEP = phosphoenol pyruvate, DHAP = dihydroxyacetonephosphate, G-3-P = glyceraldehyde-3-phosphate, F-6-P = fructose-6-phosphate, 1,3-DGP = 1,3-diphosphoglycerate, 2,3-DGP = 2,3-diphosphoglycerate, 3-PG = 3-phosphoglycerate, NADP = nicotinamide-adenine dinucleotide phosphate (TPN), NADPH = reduced nicotinamide-adenine dinucleotide phosphate (TPNH), ATP = adenosine triphosphate, ADP = adenosine diphosphate, H_2O_2 = hydrogen peroxide, GSSG = oxidized glutathione, GSH = reduced glutathione, Cyst = cysteine, Gly = glycine, Glu = glutamic acid, P_i = inorganic phosphorus.

The clinical events of the hemolytic syndrome were later defined in detail by Dern, Beutler and Alving.[47] Beutler then demonstrated that the erythrocytes of affected persons had a low content of glutathione, and that this rapidly declined further when primaquine was administered.[48] Further, *in vitro* incubation of primaquine-sensitive erythrocytes with drugs such as acetylphenylhydrazine resulted in pronounced and rapid disappearance of erythrocyte-reduced glutathione[49] and an abnormality in Heinz body production.[50] Heinz bodies are intracorpuscular inclusions, demonstrable by supravital staining with methyl violet or brilliant cresyl blue, and represent oxidatively injured and denatured hemoglobin.[51] Many drugs,[10] including sulfonamides, acetanalid, furadantin, and certain vitamin K derivatives, were soon found to precipitate hemolysis in like manner in sensitive subjects.

In 1956, Carson and his associates[11] demonstrated that the underlying defect was an inherited deficiency in the enzyme glucose-6-phosphate dehydrogenase. The same erythrocyte abnormality was subsequently shown to exist in all subjects susceptible to a hemolytic syndrome induced by the ingestion of fava beans or the inhalation of pollen from flowering fava bean plants.[52-55] Some subjects with G-6-PD deficiency can apparently eat fava beans with impunity,[56,57] and some factor other than enzyme deficiency appears required. Hemolytic susceptibility after fava bean ingestion is almost exclusively limited to the non-Negro type of deficiency.

It is now known that about 2 percent of subjects with G-6-PD deficiency have a chronic hemolytic

anemia in the absence of drug challenge,[58-60] and that infectious processes may[53] also cause hemolysis to some degree.

G-6-PD deficiency is thought to affect some 100 million people in a geographic distribution similar to that of falciparum malaria.[61,62] Among Caucasians it is common in Sardinians and in Sephardic or Oriental, but not in Askinazy or European, Jews; but the disorder has been found in almost all racial groups. About 11 percent of American Negroes exhibit the deficiency. Extensive studies have documented genetic polymorphism[63-67]; that is, many genetic variants, the result presumably of different mutations at the same locus, have now been observed and studied. For example, G-6-PD deficiency is readily demonstrable in the leukocytes of affected Caucasians,[68] but this is much less evident in Negroes. The disorder is X chromosome-linked.[10,69-71] Males and homozygous females have full expression of the abnormality and severe deficiency; heterozygous females have wide variability in the degree of enzyme deficiency, and in the severity of hemolytic episodes. The enzyme in erythrocytes may be quantitatively assayed and a spot test[72] and tests based on the diminished capacity of affected erythrocytes to reduce certain dyes[61,73] or methemoglobin are also available for use in the clinical laboratory or in survey studies in the field.

The mechanism of drug induced hemolysis in G-6-PD deficiency is thought to reside in the inability of affected cells to generate the necessary NADPH to maintain glutathione in its reduced form.[10] This results in impaired protection against a number of noxious oxidative challenges.

Clinically,[10,47] acute hemolytic anemia, jaundice and hemoglobinuria develop on the second to fourth day after ingestion of an invoking drug. Only the older cells are destroyed, but in severe instances as many as 30 to 50 percent of circulating cells may be hemolysed. Because hemolytic susceptibility is related to erythrocyte age, recovery usually takes place beginning at about the tenth day or a little later, even if the drug is continued. With continued drug administration, an equilibrium phase occurs in which there may be no anemia, and in which hemolysis referable to the destruction of cells attaining a critical age is detectable only by special erythrocyte survival studies. After discontinuance of the drug, about three or four months must elapse before an episode of comparable severity can be reinduced. This represents the length of time necessary to restore mean cell age to the pre-hemolytic status. Severity of hemolysis is dose related and drug blood level related, liver and kidney impairment being capable of affecting the latter. For more extensive and detailed discussions, the reader is referred to available reviews.[10]

6-Phosphogluconate Dehydrogenase (6-PGD) Deficiency

Brewer and Dern[75] and Parr and Fitch[76] have reported partial deficiency of 6-PGD in the erythrocytes of certain persons without hemolytic anemia. The enzyme activity was of the order of 50 percent of normal. In contrast, two cases of hereditary hemolytic anemia (those of Lauseckher and co-workers,[20] and of Scialom and colleagues[21] have been reported in which 6-PGD was reduced to about the same degree. It is, however, entirely possible that this moderate reduction was not related to the hemolytic process causally, and may have coincidentally been present with some other undetected etiologic factor.

Non-glycolytic Enzyme Deficiencies

Glutathione Reductase (GSSG-R) Deficiency

Löhr and Waller[22] have reported a kindred, certain members of which had chronic hemolytic anemia associated with a relatively severe erythrocyte deficiency in the enzyme glutathione reductase. Waller and associates[77] have also reported hematologic and neurologic difficulties associated with GSSG-R deficiency. Carson and co-workers[23] have likewise noted susceptibilty to primaquine hemolysis, but not chronic anemia, in a much less severely deficient subject. Glutathione reductase reduces oxidized glutathione and concomitantly oxidizes NADPH. It interacts with the dehydrogenases of the oxidative shunt to protect against noxious oxidative processes and to maintain the level of reduced glutathione. In sufficiently deficient states this protective mechanism is impaired.

Adenosine Triphosphatase (ATPase) Deficiency

A sodium-potassium-magnesium dependent ouabain inhibitable ATPase is generally considered to play a central role in the active transport of sodium and potassium across cell membranes. Harvald and his associates[24] have briefly reported three unrelated persons, two of whom had chronic, apparently inherited, hemolytic anemia, in whom ATPase levels in the red cell approximated half-

normal values. These workers consider it likely that ATPase deficiency and the chronic hemolytic process were related. Family studies suggested a possible dominant inheritance, but normal ATPase levels in the cells of both parents of one propositus did not conform to this hypothesis. The issue was further clouded by uncertainty as to whether the transport related ATPase or, perhaps, other forms of ATPase activity as well were involved. Additional data are required before these questions can be resolved.

Glutathione Peroxidase Deficiency

The presence of glutathione peroxidase (GSH-PX) in mammalian erythrocytes was first established by Mills.[78,79] The enzyme catalyzes the *in vitro* detoxification of hydrogen peroxide. It therefore provides protection against peroxidative injury, and is linked to HMP shunt pathway metabolism through its role in glutathione oxidation. A partial deficiency in GSH-PX has been described in association with transient mild hemolysis in the neonatal period.[80] Necheles and his associates[25] have recently described an apparently homozygous state of the enzymopathy in a Puerto Rican male in whom a hemolytic reaction developed after transfusion. After recovery, mild reticulocytosis suggested persistence of a compensated hemolytic process. The cells of the patient possessed GSH-PX activity about 25 percent of normal. The red cells of both parents exhibited about half-normal GSH-PX activity. A recessive mode of inheritance was suggested. In studies with isotopically labelled glucose, hydrogen peroxide decidedly stimulated HMP shunt activity in normal subjects, but did not do so in the patient. While it is presumed this would result in increased susceptibility to drug induced oxidative injury, data on this are thus far unreported.

Glutathione (GSH) Deficiency

A series of studies in a Dutch[26-28] kindred have demonstrated moderately severe, chronic, hereditary hemolytic anemia associated with a remarkable and nearly total absence of either oxidized or reduced glutathione. In intact erythrocytes, glyoxalase activity, for which GSH is an obligatory cofactor, was zero. As expected, the affected cells were primaquine-sensitive and, in addition, chromium, even in labeling amounts, remarkably shortened cell survival *in vivo*. When radioactive glycine, glutamine, and cysteine, the amino acid components of the tripeptide glutathione, were incubated with normal cells radioactive GSH was formed. When similar incubations were performed with the affected cells no radioactive GSH could be found. Breakdown of added radioactive oxidized glutathione occurred at an equal rate in GSH deficient and normal cells. It was concluded that a defect in GSH synthesis was probably involved. It is remarkable that such low levels of erythrocyte GSH are compatible with survival, but such has been clearly demonstrated to be the case.

Deficiencies in Embden-Meyerhof Pathway Enzymes

Pyruvate Kinase (PK) Deficiency

In 1961 and 1962 erythrocytes from certain cases of hemolytic anemia, conforming in terms of the autohemolysis test to the Type II category of Selwyn and Dacie, were assayed for all glycolytic enzyme activities. All except one — pyruvate kinase, the enzyme converting phosphoenol pyruvate to pyruvate and located just above the terminal lactate dehydrogenase step — were found to have normal or greater than normal activity.[17,18] Chart 2 indicates the pyruvate kinase reaction and the essentials of the assay system.

Since that time about a hundred documented cases of hemolytic anemia with hereditary deficiency of this enzyme have appeared in the world literature, and it appears thus far that, except for

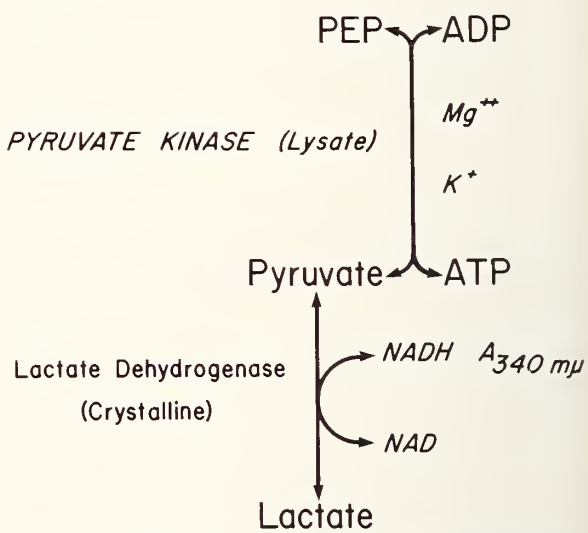


Chart 2.—Diagrammatic representation of the principles of the pyruvate kinase (PK) assay system. Substrate PEP (phosphoenol pyruvate) is provided in buffer containing ADP, Mg^{++}, and K^{+}. A dilute hemolysate provides the PK being assayed. Pyruvate generated is converted to lactate in the presence of added lactic dehydrogenase and the concomitant oxidation of NADH is followed spectrophotometrically.

G-6-PD deficiency, this is the commonest heritable disorder in the enzyme deficiency group.[29,86] Cases are of variable severity. Some patients may reach adult life partially compensated, with variable reticulocytosis and anemia and escaping transfusion. Others require transfusion from infancy and are unable to survive without donated blood. Most exhibit macrocytosis, a morphologically nondescript red cell with a scattering of cells with irregular membrane borders resembling acanthocyctes, splenomegaly and iron-containing inclusions in erythrocytes (Pappenheimer bodies) only if they have undergone splenectomy.[18]

Splenectomy only ameliorates the hemolytic process, and it was our original view that it was of little benefit. Accumulated experience[81a] has indicated, however, that removal of the spleen may be accompanied by significant improvement, sometimes with lessening or disappearance of transfusion requirements. In the severe cases of Bowman[81b,82] in an Amish population it appears that splenectomy is necessary for survival. Now we believe that splenectomy is often of distinct value and indicated, particularly when transfusions are required or anemia is significantly symptomatic. In a few cases, red cells have been morphologically bizarre,[83-85] with most cells showing numerous irregular projections of the membrane surface. Anemia is exacerbated by surgical stress and intercurrent infections.

In the commonest situation, when pyruvate kinase activity is assayed its activity is found to be greatly reduced and occasionally undetectable (though, of course, not absent) in deficient erythrocytes. Both sexes are affected, and both parents, all offspring and a number of the siblings and relatives of symptomatic subjects have on the average about one-half normal pyruvate kinase activity in their red cells. The disorder, therefore, appears to be transmitted as an autosomal recessive trait, heterozygotes being clinically and hematologically normal but biochemically detectable, and homozygotes having symptomatic hemolytic anemia.[17,18] The leukocyte pyruvate kinase activity is normal.[17,18,87,88] As would be expected with a block in terminal glycolysis, deficient cells in many instances may exhibit suboptimal glycolysis for their age,[13,30,86] may have difficulty in maintaining ATP[13,83,89-93] and NAD,[30,89,93,94] and assay of glycolytic intermediates frequently reveals abnormal accumulations of phosphoenol pyruvate, triose, particularly 2, 3-diphosphoglycerate, and even hexoses behind the point of metabolic block.[84,89,91-93,95] In such cases, pyruvate kinase, which ordinarily operates well below substrate saturation in the cell,[96] is rendered more effective by the greater availability of substrate. This compensates to some extent for the low enzyme activity characteristic of the disorder. As a result, young cell populations of homozygotes may still glycolyse actively and reasonably effectively maintain ATP levels. In some instances, defective ATP maintenance can be demonstrated by *in vitro* incubations, and similar studies may show inability to cycle NAD to NADH and back adequately. In certain cases, however, defective ATP maintenance and pronounced intermediate accumulation may not be demonstrable.[30,97,98]

It must be remembered that only metabolically affluent young cells, still capable of compensating for their glycolytic deficiency, are available for assay. As the cell ages, however, increasing accumulation of intermediates proximal to the deficient enzyme and eventual inability to generate ATP and cycle NAD are to be expected.

In most cases, the kinetics of residual enzyme activity in homozygotes has been normal. Again, such has not been universally true, and genetic polymorphism in the case of pyruvate kinase deficiency, as in G-6-PD deficiency, is becoming increasingly apparent. Instances of pyruvate kinase deficiency and abnormal enzyme kinetics have been reported by Waller and Löhr,[95] by Boivin and Galand,[99] and by Miwa.[100] Hsu, Robinson and Zuelzer[98] have intensively studied a kindred in which apparent homozygosity for pyruvate kinase activity existed in certain members with sharply differing clinical symptomatology and glycolytic intermediate patterns. In some members the characteristic hemolytic syndrome was present. In others, equally severely affected in terms of enzyme assay levels, there were no symptoms and, at most, a mild, fully compensated hemolytic process. The coexistence of two genes, undifferentiable as to their effect on pyruvate kinase in the usual assay, but with decidedly different clinical expression, was postulated.

In our laboratory, four cases of severe hereditary hemolytic anemia in two unrelated families with clinical and biochemical features of erythrocyte pyruvate kinase deficiency, but with assay values in either the normal or high heterozygote range have recently been studied by Paglia and coworkers.[101] Cases with similar intermediate or normal PK assay

values, but with the usual picture of homozygous deficiency have been noted by others.[86,88,94,100,102,103] In both families, the apparent dilemma was resolved by the finding that affected subjects had inherited from one side the "usual" gene resulting in pyruvate kinase deficiency, and from the other a gene resulting in a pyruvate kinase with grossly aberrant kinetics. The latter was characterized by remarkable catalytic inefficiency at low concentrations of its substrate, phosphoenol pyruvate, such as exist within the metabolizing erythrocyte. At high substrate concentrations (such as those employed for convenience in the usual assay) essentially no difference was evident. Heterozygosity for the kinetically abnormal gene was traceable by kinetic studies through one side of three generations in each of the two families. Not only was the K_m for the abnormal pyruvate kinase some ten times greater than that of the normal enzyme, but also differences in pH optimum and heat and storage stability were readily demonstrable. Heterozygotes had enzyme kinetics intermediate between normal subjects and the affected propositi.

The syndrome of pyruvate kinase deficiency hereditary hemolytic anemia may thus clearly result from a quantitative catalytic deficiency or, as in the above cases, from a qualitative defect of the same enzyme. With further studies it is likely that additional evidence for genetic polymorphism will be forthcoming. Sachs and coworkers[103] have likewise reported pyruvate kinase deficient hemolytic anemia in association with an enzyme catalytically inefficient at low substrate concentrations.

Triosephosphate Isomerase (TPI) Deficiency:

In 1965[31,104] and 1966[32] another highly consanguineous kindred of mixed Caucasian and Negro ancestry was studied. In members with hemolytic anemia resembling that of pyruvate kinase deficiency, a separate deficiency—that of triosephosphate isomerase—was demonstrated. In the process of anaerobic glycolysis, aldolase converts hexose diphosphate into two triose isomers, 3-phosphoglyceraldehyde and dihydroxyacetone phosphate. These are interconverted by the isomerase deficient in the erythrocytes of these subjects.

The very small number of subjects thus far studied, with the exception of one apparently unrelated case, derive from a population group with a high degree of consanguinity. While morphologically the findings are very similar to those observed in the erythrocytes of pyruvate kinase deficiency, the total syndrome, clinically and biochemically, presents many differences:[31,32,33a,33b]

- The autohemolysis test resembles that seen in hereditary spherocytosis. This is to say that substantial autohemolysis, well corrected by additives of glucose and adenosine, is observed.[31]
- Dihydroxyacetone accumulation is a prominent biochemical feature.[33a,33b]
- The enzyme deficiency is present in leukocytes, muscle and cerebrospinal fluid[33a] and possibly (though this is not yet certain) in other body tissues.
- An atypical, severe and progressive neurologic deficit, involving peripheral nerves and central nervous tissue, has been noted in the small number of affected children who have survived the first few months of life.[31,32,33a,104] This is clearly not related to kernicterus, and quite possibly may be the clinical manifestation of the isomerase deficiency in nervous tissue.
- Two unexplained sudden deaths in affected children have led to clinical suspicion (thus far unconfirmed) that cardiac muscle dysfunction may at times be a significant feature.[33a]

It is of tangential interest that sickle cell trait and G-6-PD deficiency have been demonstrated in the same kindreds, with a variety of combinations of these inherited metabolic errors and TPI deficiency.[32] Again, in TPI deficiency both sexes are involved, heterozygotes and homozygotes are definable, and an autosomal recessive mode of inheritance is indicated.[31,32,104]

Hexokinase (HK) Deficiency:

A single kindred has been extensively studied in which one child has had hemolytic anemia since birth, and in which erythrocyte, but not leukocyte, hexokinase activity is extremely low.[34,105] Erythrocyte hexokinase activity must be evaluated in the context of the fact that of all the glycolytic enzymes it exhibits by far the greatest increased activity in reticulocytes and young erythrocytes. Hexokinase activity in reticulocyte-rich cell populations is severalfold—up to ten times or more—greater than in populations of mixed age in normal blood. In the case of the propositus, despite pronounced reticulocytosis and a very young mean erythrocyte age, red cell hexokinase activity was at the lower limit of normal, and six to eight times

less than in simultaneously assayed populations of comparably young control blood. Morphologically, the hemolytic anemia was essentially similar to that observed in other erythrocyte enzyme deficiency states. Autohemolysis was modestly increased, partially corrected by glucose and better corrected by adenosine. Both glucose and fructose were phosphorylated at low rates, but mannose and galactose were metabolized much more rapidly. In both parents and three siblings, values for hexokinase were either distinctly low or at the extreme lower limits of the normal range, suggesting heterozygosity for the deficiency and, again, an autosomal recessive mode of inheritance. Presumably the patient's erythrocytes, already hexokinase-deficient in youth, with maturation and further attrition of the already impaired enzyme, soon are rendered incapable of survival.

Glucosephosphate Isomerase (GPI) Deficiency:

Four children in two unrelated kindreds[36,37,106] have now been shown to have severe hereditary hemolytic anemia associated with a deficiency of glucosephosphate isomerase, the second enzyme of the anaerobic glycolytic pathway, catalyzing the interconversion of the isomers glucose-6-phosphate and fructose-6-phosphate. Leukocytes in all four children share the deficiency. Other body tissues have not been adequately studied but, if affected, no evidence of clinical dysfunction exists. The propositi all exhibit a severe hemolytic syndrome. Splenectomy has proved of possibly some benefit, though pronounced reticulocytosis and hemolysis persist.

Again, both parents in each family and certain other family members have clearly intermediate GPI activity in their erythrocytes, and an autosomal recessive inheritance pattern again pertains. Studies with isotopically labeled glucose indicate striking impairment of recycling of fructose-6-phosphate, derived initially from pentose formed via the oxidative shunt, back through the partially blocked isomerase reaction to glucose-6-phosphate and thence again into the HMP shunt pathway. Starch gel electrophoretic studies,[107] interestingly, suggest that in the first case studied, the maternal and paternal enzyme patterns are not identical. Since both possess apparent heterozygosity for glucosephosphate isomerase deficiency, it may be that two separate mutated genes, both resulting in quantitatively deficient isomerase activity but electrophoretically different GPI protein, have been inherited by the propositus. Again, additional studies are required.

Phosphoglycerate Kinase (PGK) Deficiency:

We[38a,38b] have recently had the opportunity of studying in conjunction with colleagues from other laboratories the erythrocytes and leukocytes of a Chinese boy with lifelong hemolytic anemia. Both red and white cells exhibited severe deficiency of PGK. The hematological findings were essentially identical with those observed in other glycolytic enzyme deficiencies. There was evidence of mental retardation and behavioral aberrations, but it is not known whether or not these are related to the enzymopathy. Thus far, analysis of glycolytic intermediates is incomplete. The case is of particular interest since PGK activity was severely reduced to an estimated 4 to 5 percent of normal. The ability of erythrocytes to glycolyze and survive in these circumstances implies extensive utilization of the Rapaport-Luebering shunt or of unknown metabolic pathways. The genetics are at present obscure. The mother of the patient has a mild, compensated hemolytic process with reticulocytosis of 7 to 10 percent and suggestively low activity of PGK. The possibility of X-chromosome linkage is under consideration but unproved.

Very recently Kraus and coworkers[38a] reported an apparently similar case, characterized by chronic hemolytic anemia and PGK deficiency most evident in older erythrocytes separated by density gradient techniques. The patient had no known living relatives and genetic data could not be obtained.

2,3-Diphosphoglycerate Mutase (2,3-DPGM) Deficiency:

Bowdler and Prankerd[108] have reported an inferred 2,3-DPGM deficiency in association with hereditary hemolytic anemia. The inference was based on finding about 50 percent normal 2,3-DPGM in erythrocytes, a failure of 2,3-DPG to increase when glycolysis was inhibited *in vitro* with sodium fluoride, and very small increases of 2,3-DPG after incubations with glucose and inosine. The latter two findings were in contrast to those observed with normal cells.

Löhr and Waller[39] made similar inferences in subjects with decreased 2,3-DPG content of erythrocytes. The mutase itself was not measured di-

rectly. The indirect measurements upon which inferences are based leads to some reservations as to the conclusive nature of the findings.

Schröter[41,42] presented more convincing observations in a child with very severe nonspherocytic hemolytic anemia who died at age 3 months. Curiously, though, despite the evidence of a fulminating hemolytic process, the reticulocyte count was only slightly elevated, and serum bilirubin only in the neighborhood of one milligram percent. The child required almost daily transfusions and donated cells were also destroyed at a phenomenal rate despite inability to demonstrate any extracorpuscular mode of destruction. The constant presence of many foreign, homologous red cells in the infant's blood prevented meaningful enzyme assays in the child. However, 2,3-DPGM activity of the order of 50 percent of normal was demonstrated by direct methods in both parents, a paternal sister and a grandmother of the propositus. The results suggest that the propositus was homozygous for 2,3-DPGM deficiency, while the phenotypically healthy parents and affected relatives were heterozygous. The peculiar lack of more than slight reticulocytosis or bilirubinemia, and the rapid destruction of transfused cells remain an enigma, however.

Discussion

The presence of highly specific erythrocyte enzymopathies, genetically transmitted as either autosomal recessive or X chromosome-linked traits in a wide variety of the comparatively uncommon lifelong hemolytic anemias lends strong support to a direct cause and effect relationship. This is rendered still more likely by the glycolysis-related nature of observed deficiencies and the established unique dependence of the metabolically impoverished erythrocytes upon the glycolytic machinery. Still, certain unresolved questions clearly exist. If the enzymopathies interfere with glucose metabolism, why do *in vitro* studies at times indicate reasonably adequate glycolysis and ATP maintenance in the cells of affected subjects? Why are sharp phenotypic differences observed in the clinical severity of hemolysis in persons in different families (and sometimes in the same kindred) in the presence of *in vitro* enzyme assays indicating comparably severe deficiency? What are the ultimate mechanisms of hemolysis in deficient erythrocytes?

The answers are at present imprecise and inadequate. First, though, it must be recognized that *a priori* only those reticulocytes and young erythrocytes still capable of survival in the patient are available for study, and all metabolic parameters measured are mean values for this cell population. The metabolic capabilities of these young erythrocytes cannot be projected to define the metabolic status which hypothetically would exist at some later stage of aging. Reticulocytes and young erythrocytes possess many metabolic advantages which are lost with increasing maturity. They are able to prime the metabolic pipeline with glycolytic subtrates much more effectively than can older cells as a result of the relatively great activity of many of their glycolytic enzymes and, particularly, but not exclusively, hexokinase.[5,34,35] The reticulocyte still possesses Krebs cycle activity, the capacity for oxidative phosphorylation and the ability to generate ATP by mechanisms other than those relating to the conversion of glucose to lactate.

The metabolic impairment inherent in a severe enzymopathy is, while severe, partial and never complete. Compensatory mechanisms may in young cells, then, still permit survival. But a form of selective metabolic progeria exists. Enzymatically, in a sense, such erythrocytes are old before their time, and normal survival is not to be expected.

To determine precise preludes to destruction requires knowledge of the metabolic parameters of the older, moribund cell. Unfortunately, for obvious reasons, these crucial measurements cannot be made. Further, the deleterious effects of accumulated intermediates by feedback mechanisms are inadequately known and currently difficult to ascertain. In addition, far too little is known about qualitative and kinetic differences in the catalytic proteins deficient in these hemolytic states. It is clear that genetic polymorphism is in some instances present, and that qualitatively different enzyme molecules can vary, not only in catalytic capacity in a given assay procedure, but also in susceptibility to denaturation with aging and in catalytic efficiency at different substrate concentrations. In most cases the available data are inadequate for assessment of these properties.

Technological difficulties of *in vitro* assays likewise exist. Since broken cells are employed, enzyme stability in dilute hemolysates and under preparatory conditions are factors in many in-

stances insufficiently explored. The glycolytic sequences are composed of interlocking and interdependent reactions. When a critical, rate-limiting threshold of activity for any given enzyme is approached, the phenotypic consequences are conditioned by all the other interrelated reactions of glycolysis. Variations within the so-called normal range, ordinarily negligible, may, in the critical threshold zone, determine the ability or inability of erythrocytes to maintain their integrity and survive at any given stage in their maturation. Precise *in vitro* assay activities may, then, not *per se* correlate well with *in vivo* erythrocyte life span.

The mechanisms resulting in enzymopathies may well be diverse. A given genic defect may result in the actual lack of synthesis of enzyme protein or, alternatively, in the production of a catalytically inefficient protein with or without aberrant kinetics. In the case of some forms of G-6-PD and PK deficiencies, it is clear that the production of qualitatively abnormal proteins is operative. In many other circumstances there is no valid information. The possibility of the presence of enzyme inhibitors or absence of activators is also present, though less likely, since no evidence for these has been obtained to date. Finally, the existence of many instances of apparently heritable hemolytic anemia, resembling those associated with known enzymopathies, but in which a point of metabolic inadequacy has not been yet ascertainable, renders it certain that other defined instances of molecular disease will emerge in future investigation.

Note: Bibliographical references have been selected particularly to indicate historical priorities and comprehensive studies, and to document specific points. The vast medical literature in certain areas covered precludes complete documentation; hence some significant contributions have been omitted. These are for the most part available in the total bibliographies of the individual references cited.

REFERENCES

1. Allison, A. C., and Burn, G. P.: Enzyme activity as a function of age in the human erythrocyte, Brit. J. Haemat., 1:291, 1955.

2. Marks, P. A., Johnson, A. B., Hirschberg, E., and Banks, J.: Studies on the mechanism of aging of human red blood cells, Ann. New York Acad. Sci., 75:95, 1958.

3. Marks, P. A., Johnson, A. B., and Hirschberg, E.: Effect of age on enzyme activity in erythrocytes. Proc. Nat. Acad. Sci., 44:529, 1958.

4. Sass, M. D., Vorsanger, E., and Spear, P. W.: Enzyme activity as an indicator of red cell age. Clin. Chim. Acta, 10:21, 1964.

5. Brok, F., Ramot, B., Zwang, E., and Danon, D.: Enzyme activities in human red blood cells of different age groups, Israel J. M. Sci., 2:291, 1961.

6. Rapaport, S., and Luebering, J.: The formation of 2,3-diphosphoglycerate in rabbit erythrocytes: the existence of a diphosphoglycerate mutase, J. Biol. Chem., 183: 507, 1950.

7. Rapaport, S., and Luebering, J.: An optical study of diphosphoglycerate mutase, J. Biol. Chem., 196:583, 1952.

8. Bartlett, G. R.: Human red cell glycolytic intermediates and colorimetric assay methods for free and phosphorylated glyceric acids, J. Biol. Chem., 234:449 and 469, 1959.

9. Murphy, J. R.: Erythrocyte metabolism. II. Glucose metabolism and pathways, J. Lab. & Clin. Med., 55:286, 1960.

10. Beutler, E.: Glucose-6-phosphate dehydrogenase activity. *In* The Metabolic Basis of Inherited Disease, J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, editors, McGraw-Hill, New York, 2nd edition, 1960.

11. Carson, P. E., Flanagan, C. L., Ickes, C. E., and Alving, A. S.: Enzymatic deficiency in primaquine-sensitive erythrocytes, Science, 24:484, 1956.

12. Dacie, J. V., Mollison, P. L., Richardson, N., Selwyn, J. G., and Shapiro, L.: Atypical congenital haemolytic anemia, Quart. J. Med., 22:79, 1953.

13. Selwyn, J. G., and Dacie, J. V.: Autohemolysis and other changes resulting from the incubation in vitro of red cells from patients with congenital hemolytic anemia, Blood, 9:414, 1954.

14. de Gruchy, G. C., Santamaria, J. N., Parsons, I. C., and Crawford, H.: Nonspherocytic congenital hemolytic anemia, Blood, 16:1371, 1960.

15. de Gruchy, G. C., Crawford, H., and Morton, D.: Atypical (nonspherocytic) congenital haemolytic anemia, Proc. VII Cong. Internat. Soc. Hemat., Rome, 2:425, 1958 (part 1), Il Pensiero Scientifico, Rome.

16. Robinson, M. A., Loder, P. B., and de Gruchy, G. C.: Red cell metabolism in non-spherocytic congenital haemolytic anemia, Brit. J. Haemat., 7:327, 1961.

17. Valentine, W. N., Tanaka, K. R., and Miwa, S.: A specific erythrocyte glycolytic enzyme defect (pyruvate kinase) in three subjects with congenital non-spherocytic hemolytic anemia, Tr. A. Am. Physicians, 74:100, 1961.

18. Tanaka, K. R., Valentine, W. N., and Miwa, S.: Pyruvate kinase (PK) deficiency hereditary non-spherocytic hemolytic anemia, Blood, 18:784, 1961 (abstract). Blood, 19:267, 1962.

19. Boivin, P., Piguet, H., and Galand, C.: Anomalies des enzymes de la degradation du glucose erythrocytaire, Nouv. Rev. Franc. Hémat., 6:769, 1966.

20. Lausecker, C., Heidt, P., Fischer, D., Hartleyb, H., and Löhr, G. W.: Anémie hémolytique constitutionnelle avec deficit en 6-phosphogluconate-deshydrogenase, Arch. Franc. Pédiat., 22:789, 1965.

21. Scialom, C., Najean, Y., and Bernard, J.: Anémie hémolytique congénitale non-sphérocytaire avec déficit incomplet en 6-phosphogluconique-déshydrogenase, Nouv. Rev. Franc. Hémat., 6:452, 1966.

22. Löhr, G. W., and Waller, H. D.: Eine neue enzymopenische hämolytische Anämie mit Glutathion-reduktase-mangel, Med. Klinik, 57:1521, 1962.

23. Carson, P. E., Brewer, G. J., and Ickes, C.: Decreased glutathione reductase with susceptibility to hemolysis, J. Lab. & Clin. Med., 58:804, 1961 (abstract).

24. Harvald, B., Hanel, K. H., Squires, R., and Trap-Jensen, J.: Adenosine-triphosphatase deficiency in patients with nonspherocytic hemolytic anemia, Lancet, 2:18, 1964.

25. Necheles, T. F., Maldonado, N., Barquet-Chediak, A., and Allen, D. M.: Homozygous erythrocyte glutathione-peroxidase deficiency, Blood, 30:880, 1967 (abstract).

26. Oort, M., Loos, J. A., and Prins, H. K.: Hereditary absence of reduced glutathione in the erythrocytes—a new clinical and biochemical entity, Vox Sang, 6:370, 1961.

27. Prins, H. K., Oort, M., Loos, J. A., Zürcher, C., and Beckers, T. H.: Hereditary absence of glutathione in the erythrocytes. Biochemical, haematological and genetical studies, Proc. IX Congr. Europ. Soc. Haemat., Lisbon, 1963, p. 739 (S. Karger, Basel/New York, 1963).

28. Prins, H. K.: Oort, M., Loos, J. A., Zürcher, C., and Beckers, T. H.: Congenital nonspherocytic hemolytic anemia associated with glutathione deficiency of the erythrocytes. Hematologic, biochemical, and genetic studies, Blood, 27:145, 1966.

29. Valentine, W. N., and Tanaka, K. R.: Pyruvate kinase deficiency hemolytic anemia. *In* The Metabolic Basis of Inherited Disease, J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, editors, McGraw-Hill, New York, 2nd edition, 1966, p. 1051.

30. Keitt, A. S.: Pyruvate kinase deficiency and related disorders of red cell glycolysis, Am. J. Med., 41:762, 1966.

31. Schneider, A. S., Valentine, W. N., Hattori, M., and Heins, H. L., Jr.: Hereditary hemolytic anemia with triosephosphate isomerase deficiency, New Eng. J. Med., 272:229, 1965.

32. Valentine, W. N., Schneider, A. S., Baughan, M. A., Paglia, D. E., and Heins, H. L., Jr.: Hereditary hemolytic anemia with triosephosphate isomerase deficiency. Studies in kindreds with co-existent sickle cell trait and erythrocyte glucose-6-phosphate dehydrogenase deficiency, Am. J. Med., 41:27, 1966.

33. (a) Schneider, A. S., Valentine, W. N., Baughan, M. A., Paglia, D. E., Shore, N. A., and Heins, H. L., Jr.: (A) Triosephosphate isomerase deficiency, a multi-system inherited disorder. Clinical and genetic aspects. *In* Hereditary Disorders of Erythrocyte Metabolism, E. Beutler, editor, Grune and Stratton, New York, in press, 1968.

(b) Schneider, A. S., Dunn, I., Ibsen, K. H., and Weinstein, I. M.: (B) Inherited triosephosphate isomerase deficiency. Erythrocyte carbohydrate metabolism and preliminary studies of the erythrocyte enzyme. Ibid, 1968.

34. Valentine, W. N., Oski, F. A., Paglia, D. E., Baughan, M. A., Schneider, A. S., and Naiman, J. L.: Hereditary hemolytic anemia with hexokinase deficiency. Role of hexokinase in erythrocyte aging, New Eng. J. Med., 276:1, 1967.

35. Valentine, W. N., Oski, F. A., Paglia, D. E., Baughan, M. A., Schneider, A. S., and Naiman, J. L.: Erythrocyte hexokinase and hereditary hemolytic anemia. *In* Hereditary Disorders of Erythrocyte Metabolism, E. Beutler, editor, Grune and Stratton, New York, in press, 1968.

36. Baughan, M. A., Valentine, W. N., Paglia, D. E., Ways, P. O., Simon, E. R., and DeMarsh, Q. B.: Hereditary hemolytic anemia associated with glucosephosphate isomerase (GPI) deficiency — a new enzyme defect of human erythrocytes, Amer. Society of Hematology Meeting, Toronto, Canada, Dec. 1967, Blood, 30:850, 1967 (abstract).

37. Baughan, M. A., Valentine, W. N., Paglia, D. E., Ways, P. O., Simon, E. R., and DeMarsh, Q. B.: Hereditary hemolytic anemia associated with glucosephosphate isomerase (GPI) deficiency — a new enzyme defect of human erythrocytes, Blood, in press.

38. (a) Kraus, A. P., Langston, M. F., and Lynch, B. L.: Red cell phosphoglycerate kinase deficiency. A new cause of nonspherocytic hemolytic anemia, Biochem. Biophys. Res. Comm., 30:173, 1968.

(b) Valentine, W. N., Hsieh, H., Paglia, D. E., Anderson, H. M., Baughan, M. A., and Jaffé, E. R.: Erythrocyte enzymopathies with special reference to hemolytic anemia and a new specific disorder of glycolysis (phosphoglycerate kinase—PGK—deficiency). Unpublished data.

39. Löhr, G. W., and Waller, H. D.: Zur Biochemie einiger angeborener hämolytischer Anämien, Folia Haemat., 8:377, 1963.

40. Alagille, D., Fleury, J., and Odièvre, M.: Déficit congénital en 2, 3-diphosphoglycéromutase, Bull. Mem. Soc. Med. Hop., Paris, 115:483, 1964.

41. Schröter, W.: Kongenitale nichtsphärocytare Hämolytische Anämie bei 2, 3-diphosphoglycerate Mutasemangel du Erythrocyten im Fröhen Sauglingsalter, Klin. Wschr., 43:1147, 1965.

42. Schröter, W., and Heyden, H. V.: Kinetik der 2,3-diphosphoglycerateunsatzes in menschlichen Erythrocyten, Biochem. Zeitsch., 341:387, 1965.

43. Cordes, W.: Experiences with plasmochin in malaria: preliminary reports, 15th Annual Report, United Fruit Co. (Med. Dept.), 1926, p. 66.

44. Earle, D. P., Bigelow, F. S., Zubrod, C. G., and Kane, C. A.: Studies on the chemotherapy of the human malarias. IX. Effect of pamaquine on the blood cells of man, J. Clin. Invest., 27:121, 1948.

45. Hockwald, R. S., Arnold, J., Clayman, C. B., and Alving, A. S.: Status of primaquine. IV. Toxicity of primaquine in Negroes, JAMA, 149:1568, 1952.

46. Dern, R. J., Weinstein, I. M., LeRoy, G. V., Talmadge, D. W., and Alving, A. S.: The hemolytic effect of primaquine. I. The localization of the drug-induced hemolytic defect in primaquine-sensitive individuals, J. Lab. Clin. Med., 43:303, 1954.

47. Dern, R. J., Beutler, E., and Alving, A. S.: The hemolytic effect of primaquine. II. The natural course of the hemolytic anemia and the mechanism of its self-limited character, J. Lab. Clin. Med., 44:171, 1954.

48. Beutler, E., Dern, R. J., Flanagan C. L., and Alving, A. S.: The hemolytic effect of primaquine. VII. Biochemical studies of drug-sensitive erythrocytes, J. Lab. Clin. Med., 45:286, 1955.

49. Beutler, E.: The glutathione instability of drug-sensitive red cells: a new method for the detection of drug sensitivity, J. Lab. Clin. Med., 49:84, 1957.

50. Beutler, E., Dern, R. J., and Alving, A. S.: The hemolytic effect of primaquine. VI. An in vitro test for sensitivity of erythrocytes to primaquine, J. Lab. Clin. Med., 45:40, 1955.

51. Jandl, J. H., Engle, L. K., and Allen, D. W.: Oxidative hemolysis and precipitation of hemoglobin, J. Clin. Invest., 39:1818, 1960. Ibid., 40:454, 1961.

52. Szeinberg, A., Sheba, C., Hirshorn, N., and Bodononyi, E.: Studies on erythrocytes in cases with a past history of favism and drug-induced acute hemolytic anemia, Blood, 12:603, 1957.

53. Szeinberg, A., Asher, Y., and Sheba, C.: Studies on glutathione stability in erythrocytes of cases with past history of favism or sulfa-drug-induced hemolysis, Blood, 13:348, 1958.

54. Szeinberg, A., Sheba, C., and Adam, A.: Enzymatic abnormality in erythrocytes of a population sensitive to *Vicia faba* or drug-induced hemolytic anemia, Nature, London, 181:1256, 1958.

55. Zinkham, W. H., Lenhard, R. E., Jr., and Childs, E.: A deficiency of glucose-6-phosphate dehydrogenase in erythrocytes from patients with favism, Bull. Johns Hopkins Hosp., 102:169, 1958.

56. Sansone, G., Piga, A. M., and Segni, G.: Il favisma, Edizioni Minerva Medica, Torino, 1958.

57. Szeinberg, A., Sheba, C., and Adam, A.: Selective occurrence of glutathione instability in red blood corpuscles of the various Jewish tribes, Blood, 13:1043, 1958.

58. Newton, W. A., Jr., and Bass, J. C.: Glutathione-sensitive chronic nonspherocytic hemolytic anemia, Amer. J. Dis. Child., 96:501, 1958.

59. Shahide, N. T., and Diamond, L. K.: Enzyme deficiency in erythrocytes in congenital nonspherocytic hemolytic anemia, Pediatrics, 24:245, 1959.

60. Kirkman, H. N., and Riley, H. D., Jr.: Congenital nonspherocytic hemolytic anemia, Am. J. Dis. Child., 102:313, 1961.

61. Motulsky, A. G., and Campbell-Krant, J. M.: Population genetics of glucose-6-phosphate dehydrogenase deficiency of the red cell, Proc. Conf. Genetic Polymorphisms and Geographic Variations in Disease, Grune and Stratton, New York, 1961, p. 159.

62. Allison, A. C., and Clyde, D. F.: Malaria in African children with deficient erythrocyte glucose-6-phosphate dehydrogenase, Brit. M. J., 1:1346, 1961.

63. Kirkman, H. N., and Hendrickson, E. M.: Sex-linked electrophoretic difference in glucose-6-phosphate dehydrogenase, Am. J. Human Genet., 15:241, 1963.

64. Boyer, S. H., Porter, I. H., and Weilbacher, R. G.: Electrophoretic heterogeneity of glucose-6-phosphate dehydrogenase and its relationship to enzyme deficiency in man, Proc. Nat. Acad. Sci., U.S., 48:1868, 1962.

65. Kirkman, H. N., Brinson, G. A., and Pickard, B. M.: New variants of glucose-6-phosphate dehydrogenase in Caucasian males, Proc. IX Cong. Europ. Soc. Haemat., Lisbon, 1963, part II, S. Karger, Basel, p. 685.

66. Kirkman, H. N., Riley, H. D., Jr., and Crowell, B. B.: Different enzymic expressions of mutants of glucose-6-phosphate dehydrogenase, Proc. Nat. Acad. Sci., U.S., 46:938, 1960.

67. Marks, P. A., Banks, J., and Gross, R. T.: Genetic heterogeneity of glucose-6-phosphate dehydrogenase deficiency, Nature, 194:454, 1962.

68. Ramot, B., Fisher, S., Szeinberg, A., Adam, A., Sheba, C., and Gafni, D.: A study of subjects with erythrocyte glucose-6-phosphate dehydrogenase deficiency. II. Investigation of leukocyte enzymes, J. Clin. Invest., 38: 2234, 1959.

69. Childs, B., Zinkham, W., Browne, E. A., Kimbro, E. L., and Torbert, J. V.: A genetic study of a defect in glutathione metabolism of the erythrocyte, Bull. Johns Hopkins Hosp., 102:21, 1958.

70. Browne, E. A.: The inheritance of an intrinsic abnormality of the red cell predisposing to drug-induced hemolytic anemia, Bull. Johns Hopkins Hosp., 101:115, 1957.

71. Adam, A.: Linkage between deficiency of glucose-6-phosphate dehydrogenase and colour blindness, Nature, London, 189:686, 1961.

72. Fairbanks, V. F., and Beutler, E.: A simple method for the detection of erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD spot test), Blood, 20:591, 1962.

73. Kraus, A. P., Neely, C. L., Carey, F. T., and Kraus, L. M.: Detection of deficient erythrocyte regeneration of reduced triphosphopyridine nucleotide from glucose-6-phosphate: evaluation of a rapid screening test, Ann. Int. Med., 55:765, 1962.

74. Brewer, G. J., Tarlov, A. R., and Alving, A. S.: The methemoglobin reduction test for primaquine-type sensitivity of erythrocytes, JAMA, 180:386, 1962.

75. Brewer, G. J., and Dern, P. J.: A new inherited enzymatic deficiency of human erythrocytes: 6-phosphogluconate dehydrogenase deficiency, Amer. J. Human Genet., 16:472, 1964.

76. Parr, C. W., and Fitch, L. I.: Hereditary partial deficiency of human erythrocyte phosphogluconate dehydrogenase, Biochem. J., 93, 28c, 1964.

77. Waller, H. D., Löhr, G., Zysno, E., Gerok, W., Voss, D., and Strauss, G.: Glutathionreduktasemangel mit hämatologischen und neurologischen Störungen, Klin. Wchnschr., 43:413, 1965.

78. Mills, G. C.: Hemoglobin catabolism. I. Glutathione peroxidase, an erythrocyte enzyme which protects hemoglobin from oxidative breakdown, J. Biol. Chem., 229:189, 1957.

79. Mills, G. C., and Randall, H. P.: Hemoglobin catabolism. II. The protection of hemoglobin from oxidative breakdown in the intact erythrocyte, J. Biol. Chem., 232:589, 1958.

80. Necheles, T. F., Boles, T. A., and Allen, D. M.: Erythrocyte glutathione-peroxidase deficiency and hemolytic disease of the newborn, Blood, 28:988, 1966 (abtract).

81. (a) Nathan, D. G., Oski, F. A., Miller, D. R., and Gardner, F. H.: Life span and organ sequestration of red cells in pyruvate kinase deficiency, N. Eng. J. Med., 278: 73, 1968.

(b) Bowman, H. S., and Procopio, F.: Hereditary nonspherocytic hemolytic anemia of pyruvate kinase deficient type, Ann. Int. Med., 58:567, 1963.

82. Bowman, H. S., McKusick, V. A., and Drowamráju, K. R.: Pyruvate kinase hemolytic anemia in an Amish isolate, Amer. J. Human Genet., 17:1, 1965.

83. Oski, F. A., and Diamond, L. K.: Erythrocyte pyruvate kinase deficiency resulting in congenital nonspherocytic hemolytic anemia, New Eng. J. Med., 269: 763, 1963.

84. Nathan, D. G., Oski, F. A., Sidel, V. W., and Diamond, L. K.: Extreme hemolysis and red cell distortion in erythrocyte pyruvate kinase deficiency. II. Measurements of erythrocyte glucose consumption, potassium flux and adenosine triphosphate stability, New Eng. J. Med., 272:118, 1965.

85. Baughan, M. A., Paglia, D. E., Schneider, A. S., and Valentine, W. N.: An unusual hematological syndrome with pyruvate kinase deficiency and thalassemia minor in the kindreds, Acta Haemat., in press.

86. Tanaka, K. R., and Valentine, W. N.: Pyruvate kinase deficiency. *In* Hereditary Disorders of Erythrocyte Metabolism, E. Beutler, editor, Grune and Stratton, New York, in press, 1968.

87. Brunetti, P., Puxeddu, A., Nenci, G., and Migliorini, E.: Congenital nonspherocytic haemolytic anemia due to pyruvate kinase deficiency, Acta Haemat., 30:88, 1963.

88. Koler, R. D., Bigley, R. H., Jones, R. T., Rigas, D. A., Van Bellinghen, P., and Thompson, P.: Pyruvate kinase: molecular differences between human red cell and leukocyte enzyme, Cold Spring Harbor Symposia Quart. Biol., 29:213, 1964.

89. Busch, D.: Erythrocyte metabolism in three persons with hereditary nonspherocytic haemolytic anemia, deficient in pyruvate kinase, Proc. IX Europ. Soc. Haemat., Lisbon, 1963, vol. 2, part 1, p. 783, S. Karger, Basel.

90. Löhr, G. W.: Hämatologische enzymologie, Helvet. Med. Acta, 30:428, 1963.

91. Prankerd, T. A. J.: Inherited enzyme defects in congenital haemolytic anemias, Proc. IX Cong. Europ. Soc. Haemat., Lisbon, 1963, vol. 2, part 1, p. 735, S. Karger, Basel.

92. Shafer, A. W.: Glycolytic intermediates in erythrocytes in nonspherocytic hemolytic anemia with deficiency of glucose-6-phosphate dehydrogenase (G-6-PD) or pyruvate kinase (PK), Clin. Res., 11:103, 1963 (abstract).

93. Grimes, A. J., Meisler, A., and Dacie, J. V.: Hereditary nonspherocytic haemolytic anemia. A study of red cell carbohydrate metabolism in twelve cases of pyruvate kinase deficiency, Brit. J. Haemat., 10:403, 1964.

94. Loder, P. B., and de Gruchy, G. C.: Red cell enzymes and co-enzymes in non-spherocytic congenital haemolytic anemias, Brit. J. Haemat., 11:21, 1965.

95. Waller, H. D., and Löhr, G. W.: Hereditary non-spherocytic enzymopenic hemolytic anemia with pyruvate kinase deficiency, Proc. IX Cong. Internat. Soc. Hemat., Mexico City, 1962, Universidad Nacional Autonoma de Mexico, Mexico, D.F., p. 257.

96. Rose, I. A., and Warms, J. V. B.: Control of glycolysis in the human red blood cell, J. Biol. Chem., 241: 4848, 1966.

97. Twomey, J., Moser, R., Hudson, W., O'Neal, F., and Alfrey, C.: ATP metabolism in pyruvate kinase (PK) deficient erythrocytes, Clin. Res., 14:437, 1966 (abstract).

98. Hsu, T. H. J., Robinson, A. R., and Zuelzer, W. W.: Genetic polymorphism of hemolytic anemias associated with erythrocyte pyruvic kinase deficiency, Blood, 28: 977, 1966 (abstract).

99. Boivin, P., and Galand, C.: Constante de Michaelis anormale pour le phospho-enol-pyruvate au cours d'un déficit en pyruvate-kinase erythrocytaire, Rev. Franc. études clin. et biol., 12:372, 1967.

100. Miwa, S.: Personal communication.

101. Paglia, D. E., Valentine, W. N., Baughan, M. A., Miller, D. R., Reed, C. F., and McIntyre, O. R.: Identification of an isozyme of pyruvate kinase (PK) responsible for hereditary hemolytic anemia, American Society of Hematology Meeting, Toronto, Canada, Dec. 5, 1967, Blood, 30:881, 1967 (abstract).

102. Busch, D., Witt, I., Berger, M., and Künzer, W.: Deficiency of pyruvate kinase in the erythrocytes of a child with hereditary non-spherocytic hemolytic anemia, Acta Paed. Scand., 55:117, 1966.

103. Sachs, J. R., Wicker, D. J., Gilcher, R. O., Conrad, M. E., and Cohen, R. J.: PK deficient hemolytic anemia inherited as an autosomal dominant, American Society of Hematology Meeting, Toronto, Canada, Dec. 5, 1967, Blood, 30:881, 1967 (abstract).

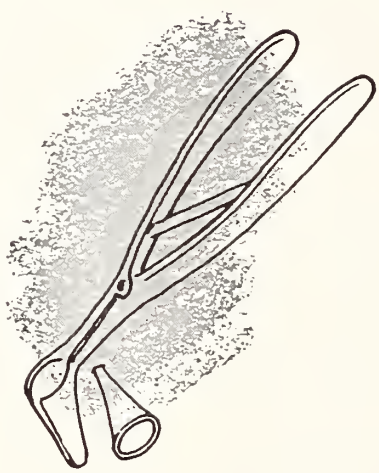
104. Shore, N. A., Schneider, A. S., and Valentine, W. N.: Erythrocyte triosephosphate isomerase deficiency, J. Pediat., 67:939, 1965.

105. Valentine, W. N., Oski, F. A., Paglia, D. E., Baughan, M. A., Schneider, A. S., and Naiman, J. L.: Erythrocyte hexokinase and hereditary hemolytic anemia. *In* Hereditary Disorders of Erythrocyte Metabolism, E. Beutler, editor, Grune and Stratton, New York, in press, 1968.

106. Paglia, D. E., Holland, P., Valentine, W. N., and Baughan, M. A.: Unpublished data.

107. Detter, J. C., Ways, P. O., Giblett, E. R., Baughan, M. A., Hopkinson, D. A., Povey, S., and Harris, H.: Inherited variations in human phosphohexose isomerase, Ann. Human Genet., in press, 1968.

108. Bowdler, A. J., and Prankerd, T. A. J.: Studies in congenital non-spherocytic hemolytic anemias with specific enzyme defects, Acta Haemat., 31:65, 1964.



MEDICAL STAFF CONFERENCE

Congenital Adrenal Hyperplasia due to 17-Hydroxylase Deficiency

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. BIGLIERI*: During the past year, our group has been fortunate in being able to study a patient representing a newly described form of congenital adrenal hyperplasia.[1] She was referred to the Clinical Study Center (USPHS-FR-83) at San Francisco General Hospital by her physician because of hypokalemic alkalosis and hypertension. Primary aldosteronism was strongly suspected.

The salient clinical features are described in Table 1. The patient is 36 years of age. She has had numerous "flu-like" syndromes and upper respiratory infections most of her life. On two occasions before the age of ten she lost consciousness during an upper respiratory infection with high fever. Prompt admittance to hospital and administration of intravenous fluids effected rapid improvement. Hypoglycemia was suspected. Following tonsillectomy at age 15 she had ten days of nausea and vomiting. The patient said that she had been told she was hypertensive at age seven. At 16 years hypertension was well established and has been well documented over the subsequent 20 years. During high school, nursing school and subsequent appointments diastolic blood pressure was at least 100 mm of mercury. Five years ago systolic blood pressure rose above 200 mm and the diastolic pressure was 120 mm. Two years ago loss of stamina and polyuria were noted by the patient. Primary amenorrhea has been a constant feature. Hypertension, weakness, and amenorrhea at first appeared to be unrelated findings, but this proved not to be so. It is of considerable interest that during a "flu-like" illness which her mother and an 11-months-old sister had at the same time, only the patient survived. On that occasion she had been put into a hospital, where intravenous fluids were given.

The patient is tall, having continued to grow until the 26th year. The skin is fine with slight malar pigmentation. She has features of hypogonadism. Axillary and pubic hair is absent. Examination of the fundi reveals only mild tortuosity of the retinal vessels. The Trousseau sign is positive and has always been positive whenever her blood pressure has been taken. Breasts are prepubertal and external genitalia are infantile. The uterus and ovaries were not palpated. No abdominal bruit nor edema has been noted.

The sella tursica, intravenous pyelogram, hemoglobin and hematocrit were within normal limits. She had persistent eosinophilia. Renal function, thyroid function, carbohydrate tolerance and blood volume were also within normal limits. Persistent hypokalemia (2.7-3.2 mEq/L) and alkalosis (pH 7.52) were demonstrated repeatedly.

*Edward G. Biglieri, M.D., Associate Professor of Medicine.

TABLE 1.—*Salient Clinical Features of 17 Hydroxylase Deficiency*

History
1. 36 year old female
2. Frequent upper respiratory infections
3. Hypoglycemic episodes during childhood
4. Hypertension 20 years
5. Primary amenorrhea
6. Weakness two years
7. Both mother at 28 and sister at 11 months died during "flu-like" illness

Physical Examination
1. Blood pressure 240/140 mm Hg (lying), 194/120 mm Hg (standing)
2. Fine skin, slight malar pigmentation, hard ears
3. Absent axillary and pubic hair
4. Fundi-mild tortuosity of vessels
5. Positive Trousseau sign
6. Absent secondary sexual characteristics
7. No abdominal bruits
8. No edema

Laboratory
1. Electrocardiogram—Flat T waves and U waves, left ventricular hypertrophy
2. Hematocrit 40 percent, Hemoglobin 13.5 gm per 100 ml
3. Eosinophilia 2-6 percent
4. BUN 12 mg/100 ml. FBS 85 mg/100 ml
5. Serum sodium 141-147 mEq/L
 Serum potassium 2.7-3.2 mEq/L
 Serum chloride 95-102 mEq/L
 Serum CO_2 29-32 mEq/L
6. Exchangeable potassium reduced at 29 mEq/Kg
7. Serum pH 7.5
8. Genotype was 46/XX

When urinary steroids were measured we received quite a surprise (Table 2). There were no 17-hydroxysteroids, 17-ketosteroids or metabolites of Compound S. Initially a measurement of 5 mg in 24 hours was obtained for the 17-ketosteroids, but this was presumably due to the enormous amounts of interfering steroids. The typical lavendar color of the Zimmerman reaction was replaced by a muddy brown color. Pregnanetriol, another 17-hydroxylated steroid, was also absent. The non-17-hydroxylated steroids, desoxycorticosterone (DOC) and corticosterone (Compound B), were considerably elevated, but aldosterone was absent. Follicle stimulating hormone was elevated, plasma renin activity was absent, and plasma ACTH increased. Treatment consisted of small doses of dexamethasone. The patient will be presented now. (Patient enters.)

DR. BIGLIERI: Will you tell the audience how you felt when taking dexamethasone?

PATIENT: You mean the lack of colds and so forth? I noticed for the first time in my memory that I did not have any sores on my lips; also, I have not been fighting a cold or upper respiratory infection since treatment was started.

TABLE 2.—*Basal Steroid Values in Present Case*

17 Hydroxylated Steroids	
17 hydroxysteroids (normal 4-10 mg/24 hr.)	0
Tetrahydro Compound S (11 desoxycortisol) (normal less than 100 mg/24 hr.)	0
17 Ketosteroids (normal 5-15 mg/24 hr.)	less than 1 mg
Pregnanetriol (normal 0.3-1.3 mg/24 hr.)	0
Non-17 Hydroxylated Steroids	
DOC (normal 50-250 μg/24 hr.)	5,240 μg/24 hr.
Compound B (Corticosterone) (normal 0.9-4.6 mg/24 hr.)	114 mg/24 hr.
Aldosterone (normal 50-168 μg/24 hr.)	0

DR. BIGLIERI: This is interesting because it is also the first time in her life that she has had normal blood pressure, normal potassium and normal steroid levels. Dr. Williams, would you like to ask any questions?

DR. ROBERT H. WILLIAMS*[1]: Dr. Biglieri gave me the opportunity of seeing this patient yesterday and reviewing all the data. I am not going to take time to comment on it, but I do want to extend enormous congratulations to him for this work. I would like to ask this question. I remember that one of her complaints was weakness. There are many reasons why this could be. Is her static strength normal? In other words, I can visualize that a particular job with repetitious movements might cause fatigue more rapidly than normal.

DR. BIGLIERI: In general, in all patients that we have seen with primary aldosteronism, which may very well be likened to this case, loss of stamina is noticed first. (The patient leaves.)

DR. WILLIAMS: She also has an absence of androgens. To what extent might that affect the situation?

DR. BIGLIERI: I think this is hard to assess, since androgens have been lacking throughout her life. The complaint of weakness and tiredness is relatively new. I think she has adjusted well to this lack of anabolic steroids, and it is the hypokalemia

*[1]Robert H. Williams, M.D., Professor of Medicine, University of Washington.

and the potassium depletion that have accounted for her problems. I might add that when we did measure her exchangeable potassium it was 29 mEq per kilogram which was quite reduced (normal=about 40 mEq/kg). We were quite surprised, of course, to find that the metabolites of Compound B and DOC were the only steroids present in this patient's urine, and that the blood level of Compound B was 22 to 55 micrograms per 100 ml. Normally, it is less than 1 microgram per 100 ml. To determine the metabolism of this compound, we injected labeled corticosterone and found the half-time of disappearance to be 50 to 60 minutes (normal 60 minutes). Thus, she metabolized corticosterone normally, and from this we were able to calculate the pool size. The pool size of corticosterone normally is less than 0.5 mg. In someone receiving large amounts of ACTH the pool size may increase to 4 to 8.3 mg, as we observed in this patient. The positive nitrogen balance and normal growth indicate the lack of significant catabolic action of Compound B.

Chart 1 summarizes the steroid biosynthetic pathways and points out the steroids that are present and absent (rimmed in black) in this patient. The key position of 17-hydroxylation is designated. A deficiency of this enzyme would lead to a reduction of all the steroids to the right. Those steroids not dependent on this enzyme are to the left.

Progesterone is normally hydroxylated to 17-alpha-hydroxyprogesterone and pregnanetriol is its urinary metabolite. The patient had no pregnanetriol. 17-hydroxyprogesterone is converted after 21-hydroxylation to Compound S (11 desoxycortisol). Its urinary metabolite was absent in the patient. Cortisol, the final product of this biosynthetic pathway, was also absent. This hydroxylation in the 17 position is not only a key in the synthesis of adrenal steroids, but also of ovarian steroids. The lack of breast development and maturation of the genitalia, and the absence of other estrogen effects can be accounted for by the lack of this enzyme in the ovaries. The urinary metabolites androsterone, etiocholanolone and dehydroepiandrosterone contribute ketosteroids to the urine, and these were all virtually absent. We have the absence of the key hydroxylation step for both adrenal biosynthesis of 17-hydroxylated steroids and the ovarian biosynthesis of testosterone and estrogen. This single biochemical lesion accounts for all the features that we have seen in this patient. We know she has progesterone, for we find normal amounts of pregnanediol in the urine. We have not identified as yet all the steroid metabolites of progesterone in her urine. Progesterone is 21-hydroxylated to DOC, which she has in increased amounts, and DOC is 11-hydroxylated to corticosterone. She has enormous amounts of corticosterone. Corticosterone is most likely converted to aldosterone through the formation of 18-hydroxy B (see Chart 1). Dr. Stanley Ulick was

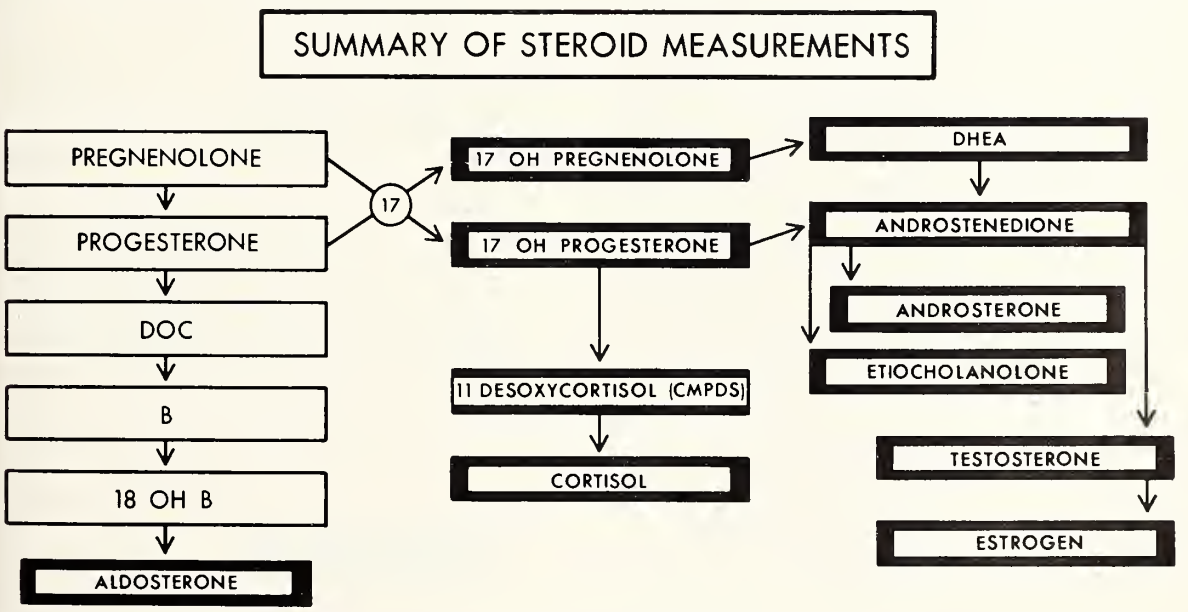


Chart 1.—Steroid measurements in patient presented. Circled 17 represents site of 17 hydroxylase step. Steroids rimmed in black were absent in the patient.

kind enough to measure the metabolite of 18-hydroxy B for us and reported the value to be one of the highest he has seen.[4] 18-B has very little salt-retaining and potassium-excreting properties. The patient also demonstrates an inability to convert 18-hydroxy B to aldosterone. The question of whether this is a separate defect in addition to 17-hydroxylase defect, or secondary inhibition of secretion of renin by Compound B or DOC, or intra-adrenal inhibition is gradually being resolved. On treatment with dexamethasone, aldosterone secretion gradually rose to 30.7 μg in 24 hours and eventually to 112 μg as DOC and Compound B secretion returned to normal. A similar pattern was observed in a second case of this disorder from UCLA. In that case, after treatment with pituitary suppression for one week plasma renin activity and aldosterone production returned to normal.[3] Thus, the suppression of aldosterone production was not due to a second enzymatic defect. While reduction of plasma renin activity due to Compound B and DOC is suggested as the mechanism for the reduction of aldosterone, a more dominant mechanism may exist. This conjecture is based on the observation that continued administration of ACTH to patients with aldosterone-producing tumors who lack plasma renin activity leads to reduction of aldosterone production. This suggests that with chronic ACTH overproduction an intra-adrenal event may be the key to inhibition of aldosterone biosynthesis.[2]

The mineralocorticoids present in this patient have little glucocorticoid or anti-inflammatory action. They do not have any suppressive effect on the pituitary. They do not affect eosinophils, and it is of interest that the eosinophils in this patient were increased. Since she is unable to suppress ACTH, the therapy was quite clear here — small doses of dexamethasone to supress ACTH (Chart 2). Treatment consisted of 1 to 2 mg of dexamethasone daily. The elevated levels of DOC and Compound B returned to normal values and aldosterone production eventually (six months) returned to normal (Chart 3). Dexamethasone produced prompt diuresis of sodium, retention of potassium, correction of hypokalemic alkalosis and restoration of normal blood pressure within one week. When treatment was stopped, Compound B and DOC secretion promptly rose to previous levels, sodium was retained, potassium was lost and hypertension returned. It was fascinating to observe a person who has had documented hypertension most of her life who could be made normotensive with just small doses of dexamethasone. At present her blood pressure is 130/80 mm of mercury.

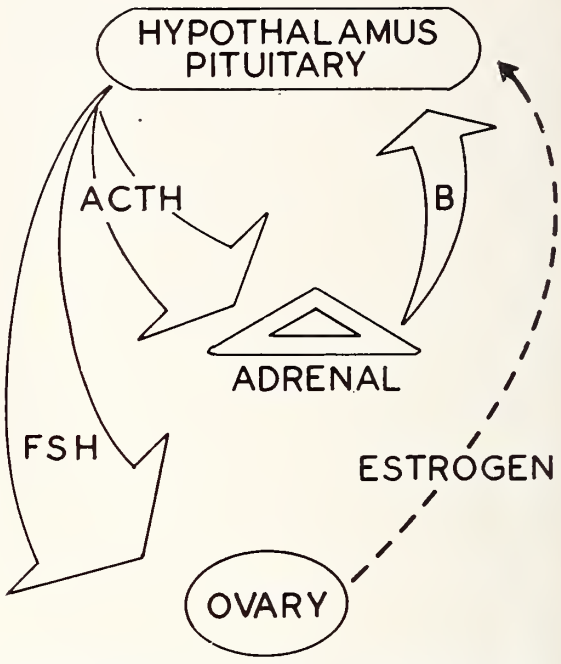


Chart 2.—Pituitary-adrenal-ovarian axis in man. FSH = follicle stimulating hormone, B = corticosterone, ACTH = adrenocortical stimulating hormone.

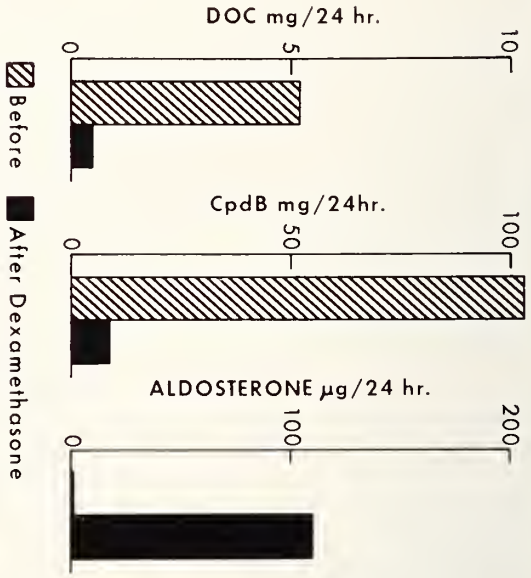


Chart 3.—Effect of dexamethasone therapy on steroid levels in the patient. For abbreviations see text.

The patient's disorder represents a deficiency of 17-hydroxylase activity both in the adrenal glands and the ovaries. The lesion prevents her from making any cortisol of adrenal origin but allows the production of enormous quantities of Compound B and DOC. Compound B and DOC, as we have pointed out, have no effect on suppression of ACTH release. ACTH release is uninhibited as it increases, and a cycle is produced with increased ACTH secretion and increased Compound B and DOC. This patient emphasizes the fact that man can survive on Compound B and DOC alone. Though she survived on Compound B and DOC alone, she has not survived very well. The lack of anti-inflammatory and gluco-corticoid activity may have accounted for her life-long history of upper respiratory infections, and as she mentioned, she has had none during the last three months of treatment. These findings point out that Compound B has little or no effect on suppression of the pituitary. The eosinophilia is a reflection of the absence of cortisol. These studies demonstrate that Compound B and DOC in enormous quantities can cause suppression of renin production. They also point out that Compound B and DOC in large amounts may lead to a clinical disorder similar to primary aldosteronism. When we first saw the patient, her symptoms were indistinguishable from those of primary aldosteronism.

This enzyme defect is also present in the ovary. The patient is unable to make 17-hydroxyprogesterone and eventually other androgens and estrogens produced by the ovaries. The lack of estrogens would allow excessive secretion of follicle-stimulating hormone. These studies strongly suggest that the 17-hydroxylase enzyme may be the same enzyme in both the adrenals and the ovary (Chart 2).

Finally, to tell you briefly about her therapy: She is taking 1 mg of dexamethasone a day. This was quite adequate for several months until a craving for salt developed and serum potassium rose alarmingly. During this period mineralocorticoid lack was demonstrated, and at least in this short period aldosterone secretion had not been restored. Prolonged therapy with cortisol was more effective because of the minimal mineralocorticoid effect, and aldosterone production gradually returned.

DR. SMITH*[2]: I hope that everyone realizes what a splendid contribution Dr. Biglieri has made to endocrinology in the elucidation of this patient's disease. This is a very important case in the understanding of steroid synthesis. More specifically, it is really a form of adrenogenital syndrome which presents perhaps the first evidence that the hydroxylase enzyme is under the same genetic control in both glands. This clinical and hormonal study has ramifications which spread quite far indeed. Are there any comments or questions at this point?

PHYSICIAN IN AUDIENCE: Have urinary steroid levels of family members been determined?

DR. BIGLIERI: Unfortunately, the mother and one sibling have died. The patient is leaving for her home tomorrow and she will bring back to us an aliquot of her father's urine.

DR. JAMES HOPPER*[3]: Has a serum electrophoretic study been done?

DR. BIGLIERI: Serum proteins are normal. I do not believe that we have done an electrophoretic study.

DR. FELIX KOLB*[4]: Did she have hypoglycemia? Why did you pick dexamethasone for treatment?

DR. BIGLIERI: We have not demonstrated hypoglycemia. I picked dexamethasone because I am a purist and wanted a pure glucocorticoid hormone. I wonder now if the treatment of choice may very well be cortisol, since the patient is so sensitive to salt-retaining substances.

REFERENCES

1. Biglieri, E. G., Herron, M., and Brust, N.: 17 hydroxylation deficiency in man, J. Clin. Invest., 45:1946-1954, 1966.

2. Biglieri, E. G.: Intra-adrenal modulation of mineralocorticoid secretion, Australia Endo. Society, Aug. 1967.

3. Goldsmith, O., Solomon, D. H., and Horton R.: Hypogonadism and mineralocorticoid excess, New Eng. J. Med., 277:673, 1967.

4. Ulick, S., Gautier, S., Vetter, K. K., Markello, J. R., Yaffe, S., and Lowe, C. U.: An aldosterone biosynthetic defect in a salt losing disorder, J. Clin. Endocr., 24:669, 1964.

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*[3]James Hopper, M.D., Professor of Medicine.

*[4]Felix O. Kolb, M.D., Associate Clinical Professor Medicine & Assoc. Res. Phys. Metabolic Unit.

CASE REPORTS

Spontaneous Regression of Orbital and Facial Hemangioma

WILLIAM A. YANCEY, M.D., *San Diego*

SPONTANEOUS REGRESSION of hemangioma is well documented by Kingery,[1] Margileth,[2] and Moss.[3] The purpose of this presentation is to report a case in which the phenomenon is shown with extraordinary clarity.

Kingery said that capillary hemangiomas will regress with no treatment, but those of the cavernous type usually persist and operation may be necessary.

In Margileth's experience, 76 percent of cutaneous hemangiomas had regressed within seven years.

Moss reported 28 hemangiomas in his series, seven being infants. In four cases regression occurred without any treatment.

In the case presented here, the patient, first seen at four months of age, had a hemangioma in the orbit, periorbit and naries (Figure 1). The lesion was so large that it caused proptosis, and the cornea was not covered sufficiently to prevent exposure keratitis.

Consultation with the various tumor boards resulted in the opinion that the eyelid should be taped shut during sleep to protect the cornea. It was decided simply to observe the patient to determine whether the hemangioma became worse or better.



Figure 1.—Hemangioma in orbit, periorbit and naries in four-months-old infant. Inset shows regression two years later, without treatment.

The child was seen two years later in Baja California, while the author was on a trip with the Flying Samaritans. The hemangioma regressed (without any treatment) to such an extent that the globe had receded into the orbit and the lids functioned sufficiently well to protect the cornea (see inset, Figure 1). Also, the child appeared to have fusion and good extraocular muscle function in all fields of gaze.

This case might serve to illustrate to apprehensive parents the rewards of patiently awaiting spontaneous regression of an hemangioma in a child.

Submitted 17 July 1967.

Reprint requests to: 2290 Sixth Avenue at Juniper, San Diego 92101.

REFERENCES

1. Kingery, Frederick: Involuting hemangioma, JAMA, 194:187, 11 Oct. 1965.

2. Margileth, A.: Cutaneous hemangioma in children, JAMA, 194:523-6, 1 Nov. 1965.

3. Moss, Hugh: Expanding lesions of the orbit, Amer. J. Ophthal., 54:763, Nov. 1962.

Infantile Cortical Hyperostosis And Giant Cell Hepatitis

F. R. MARGOLIN, M.D., AND
J. H. KUSHNER, M.D., *San Francisco*

INFANTILE CORTICAL HYPEROSTOSIS (ICH) was first described by Röske[20] in 1930. By 1956, more than a hundred cases had been published[7] and many additional examples have been reported since. In nearly all documented cases, onset was at less than 6 months of age, with onset reported *in utero* in five patients, three of whom showed typical roentgenographic changes at birth[10] or during the last trimester of gestation.[3,4,14]

We recently observed a newborn infant in whom giant cell hepatitis, documented by biopsy, was associated with typical clinical and roentgenographic findings of ICH. No cases have been reported in the literature in which the characteristic osseous changes of ICH were associated with jaundice or active liver disease. This unusual association of two diseases, both of unknown but possibly viral cause, prompts this case report.

Report of a Case

The mother, a para II gravida IV had pneumonia during her fourth month of pregnancy, and had a past gestational history which included one stillborn, one normal and one Rh-erythroblastotic infant who required an exchange transfusion. Both parents, several years previously, had had infectious mononucleosis associated with an elevation of serum glutamatic oxaloacetic transaminase (SGOT), thought to represent associated hepatitis. Because of a rising maternal Coombs antibody titer to 1:16, amniocentesis was performed at 37 weeks of gestation and showed a decided elevation of the 450μ peak. At 38 weeks, after an induced but uncomplicated labor, a female infant weighing 6 pounds 9 ounces was delivered on 25 April 1964. At birth, the presence of a mild degree of erythroblastosis was confirmed by a positive Coombs test, but there was neither anemia nor a rapid elevation in serum bilirubin during the neonatal period.

On physical examination, however, pronounced ulnar deviation of both hands at the wrist, which produced a rather grotesque deformity, was observed. There was also a decided tubelike thickening of both lower extremities with firm, fixed induration of overlying soft tissue. (See Figure 1.) Radial deviation at the wrist was very limited, but the range of motion in both lower extremities was normal. Roentgenograms taken on the second day

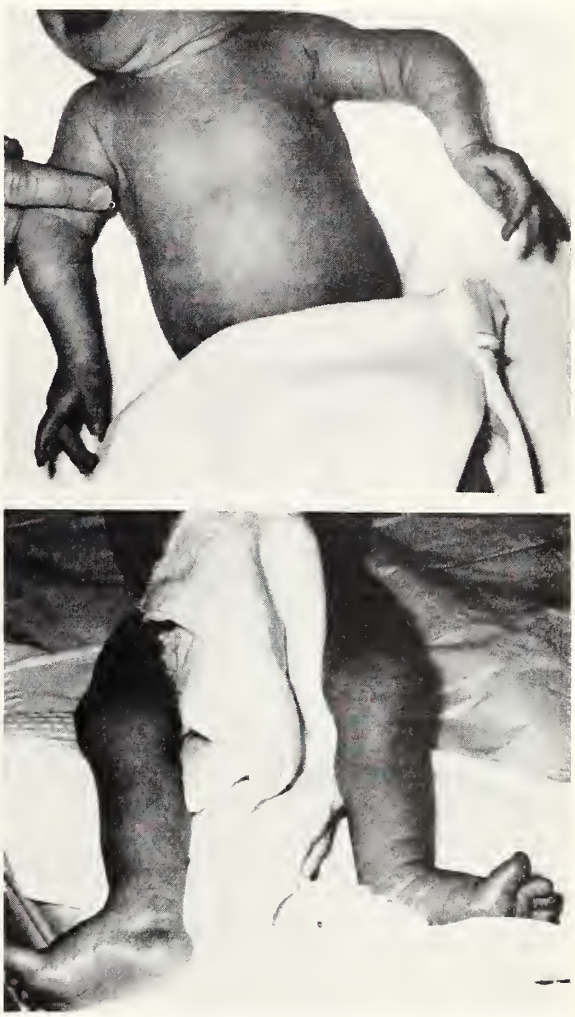


Figure 1.—Appearance of extremities at birth. Soft tissue thickening with brawny edema and ulnar deviation of the hands are evident. There is tubular thickening of both lower extremities.

From the Department of Radiology and the Department of Pediatrics, University of California-San Francisco Medical Center, San Francisco.

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of life showed a loss of tubulation, increased density and widening of the humeri, radii, ulnae, tibiae, fibulae and the right femur consistent with the radiographic findings of ICH (Figure 2). There was no evidence of disease in the mandible, clavicles, scapulae or any of the ribs. A serological test for syphilis was negative, prenatally in the mother as well as postnatally in the infant.

During her hospital stay, the infant had continued slight elevation of bilirubin, with a maximum value of 6.4 mg per 100 ml, of which 2.7 mg was direct. The stools remained light-colored and the urine quite dark, suggestive of early biliary atresia or giant cell hepatitis. On the third day of life the serum glutamic pyruvic transaminase (SGPT) was 45 (normal 5 to 35) and alkaline phosphatase 7 (normal 2 to 6) SJR units. Urine urobilinogen was negative at dilutions of 1:5 and a small amount of bile was present in the urine. The patient progressed well clinically, and the bilirubin values and jaundice appeared to stabilize, then decline, and she was discharged on the seventh day of life.

When she was seen as an outpatient, jaundice appeared to be increasing again and, indeed, the total bilirubin had risen to 16.0 mg per 100 ml (6.8 mg indirect, 9.2 mg direct), without a concomitant fall in hemoglobin. She was re-admitted to the University of California Medical Center on 19 May 1964, at 24 days of age.

At this time, the liver and spleen were noted to have become palpably enlarged. Laboratory studies confirmed persistently high but fluctuating hyperbilirubinemia. There was a gradual rise in SGPT from 45 to 350 units, in alkaline phosphatase to 15 SJR units and in bilirubin to a maximum of 18.6 mg per 100 ml, of which 11.4 g was direct. There was absence of fecal and urine urobilinogen and the urine was strongly positive for bile. Results of three urine tests for cytomegalic inclusion bodies were negative, as were tests for toxoplasmosis in both the mother and infant. Funduscopic examination of the infant showed no abnormality. An I^{131} rose bengal test showed no excretion of the radio-tagged dye into the gastrointestinal tract, suggesting a complete biliary obstruction. Liver and spleen became further enlarged and were palpated 6 cm below their respective costal margins, and a prominent venous abdominal pattern developed. The direct Coombs test remained weakly positive. The mild erythroblastosis fetalis disease continued, but no anemia developed, as the increased blood destruction was compensated for by the moderate reticulocytosis.

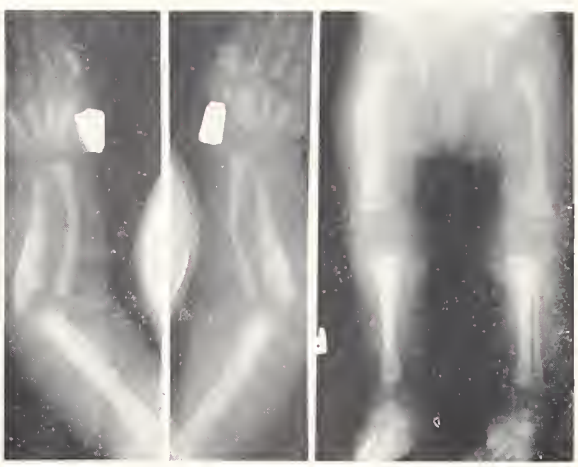


Figure 2.—The long bones at two days of age show loss of tubulation, prominent cortical thickening and bowing. The process is symmetrical except for the sparing of the left femur.

The patient received a short trial of Decholin® (sodium dehydrocholate) and corticosteroids, without significant alteration in the clinical progress of the disease. While the patient was receiving steroids, however, the SGPT fell from 340 units to 233 units over a period of 17 days. Cultures for virus on monkey kidney tissue showed no growth.

With a preoperative diagnosis of either biliary atresia or giant cell hepatitis, laparotomy was carried out 5 June and an operative cholangiogram showed a normal extrahepatic biliary tree. Biopsy of a specimen of the liver showed the presence of giant cell hepatitis. A simultaneous biopsy of the ulna, which radiologically and clinically appeared to be involved, showed "bone with a zone of dense fibrous periosteal reaction," and "several irregular fragments of the bone and periosteum demonstrated very vigorous osteoblastic activity." The patient was discharged on 17 June, 12 days later, after an uncomplicated postoperative course.

On follow-up examination at eight months of age, (28 December 1964), and again at age 20 months, (28 December 1965), the infant was observed to be retarded in physical development (below the third percentile) but was otherwise grossly normal. Repeat roentgenograms of the long bones at eight (Figure 3) and 20 months (Figure 4) showed regression of the previously noted skeletal changes. Except for some very mild residual bowing, the long bones had returned clinically and roentgenographically to normal by 20 months of age.

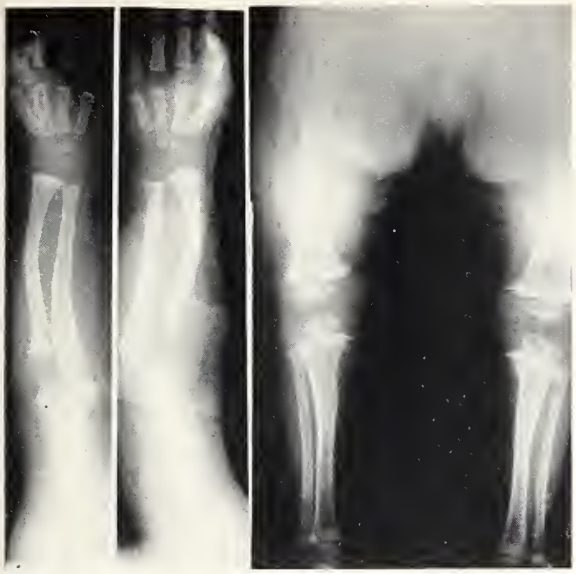


Figure 3.—At age eight months, the hyperostosis has disappeared. Tubulation and moderate bowing persist.



Figure 4.—At age 20 months, only slight bowing remains. The bones are otherwise normal. A supracondylar process is present in the distal humerus bilaterally

Comment

A review of the literature for association of simultaneous neonatal bone and liver disease disclosed only one brief mention of an infant with hepatitis and bone disease (of unknown type), who died at three months of age (seen in South America by Dr. Edith Potter). At autopsy in that case, severe osteoporosis with pronounced bony fragility and proliferation of subcortical new bone was described. Although clinical data and roentgenograms were not included in the report, Dr. Potter illustrated the histological pathologic features of the long bones of this infant in her textbook[18] as possibly associated with ICH. She knew of no other case in which the osseous changes typical of ICH were found in definite association with simultaneous neonatal hepatitis.[19]

The roentgenologic changes of the long bones of the patient in the present case at two days of age are consistent with those observed in neonates and older infants with ICH. Although the absence of mandibular involvement is somewhat unusual, Caffey[9] reviewed the films of this patient and found them to be consistent with the diagnosis of ICH.

Gradual regression of the bony changes of ICH occurs in most patients, but some residual medullary expansion and cortical thickening may persist. Bony fusion between the radius and ulna, between tibia and fibula and between adjacent ribs has been described.[16] Aside from mild residual bowing of the long bones, the skeletal changes in the patient in the present case had regressed substantially by eight months of age (Figure 3) and the only evidence of bone disease was the minimal bowing which persisted at age 20 months (Figure 4).

Because ICH can be recurrent, chronic or (rarely) even fatal, Caffey[7] recommended therapy with corticosteroids since even severely ill patients so treated became asymptomatic within several days. What effect the administration of small amounts of corticosteroids in the present case may have had on the healing of the osseous lesions is not known.

The cause of ICH remains unknown. There has been much speculation about a possible viral or low-virulence bacterial infection.

Barba and Freriks[3] suggested intrauterine osseous ischemia as a possible etiologic factor; allergy, trauma, and hormonal disturbance have also been suggested as possible etiological agents.

There have been 14 recorded cases in which ICH has occurred among siblings or in more than one member of the same family.[4] These examples of the disease in family members, the demonstration of the disease *in utero* or at birth and the limitation of postnatal onset to the first six months of life might suggest a maternal source. Genetic transmission by an autosomal recessive or autosomal dominant gene with reduced penetrance has also been suggested[4] by these same observations.

Although many observers favor a viral etiologic

factor in ICH, there is insufficient evidence to prove this theory. According to Neuhauser,[17] cases of ICH appear to have diminished in frequency in recent years. If this observation is valid, there is no readily apparent explanation.

The antecedent history of maternal hepatitis in case of neonatal giant cell hepatitis, as in the patient here reported upon, has been observed several times. There are several reports of hepatitis with giant cell formation in the infants of mothers in whom viral hepatitis developed during pregnancy. Stokes and coworkers[24] demonstrated the infectivity of giant cell hepatitis by injection of blood from an affected infant and its apparently healthy mother into volunteers. Aterman[2] marshalled these observations in support of a probable viral cause for giant cell hepatitis. By hypothesizing a modification of the virus during its passage through the mother, he explained the pathologic spectrum of neonatal giant cell hepatitis ranging from acute fulminant necrosis to chronic hepatitis with minimal fibrous scarring.

Garces and Leiva[12] reported neonatal hepatitis with giant cell transformation in both members of a pair of monozygotic twins. Wong and coworkers[25] however, described it in only one member of each of four pairs of dizygotic twins. These latter reports are somewhat difficult to reconcile with the transplacental viral transmission theory.

Hsia and associates[13] postulated a genetic etiologic lineage for giant cell hepatitis and presented data supporting an autosomal recessive mode of inheritance. Danks and Bodian[11] suggested a mutant autosome gene in homozygous form as the etiologic factor but admitted that viral agents might influence the manifestations of the neonatal hepatitis in infants homozygous for the mutant gene.

It would seem, therefore, that there is some evidence to support both the viral and genetic concepts in the etiology of both giant cell hepatitis and ICH. At present however, the cause of both disorders remains unknown.

While the Rh incompatibility in the patient in the present case contributed to her jaundice, it is doubtful that the mild erythroblastosis was responsible for either the bone disease (ICH) or the giant cell hepatitis. Neither Shorter[21,22] nor Potter[18] found any giant cells in the liver of infants with erythroblastosis. Skeletal roentgenograms in 100 infants with erythroblastosis[5] showed radiolucent metaphyseal band formation in 22, but no evidence of sclerosis or hyperostosis suggestive of ICH.

The possible role of giant cell hepatitis or ICH in causing the sharply elevated 450μ peak on amniocentesis, typical of far more severe erythroblastosis than was observed in this case, is intriguing. Such false-positive results on amniocentesis have been found in neonates with hepatitis.

Decided osteoporosis, fragile bones and roentgenographic changes suggestive of rickets have been described in older neonates with biliary atresia.[15] Periosteal new bone formation of the type seen in ICH, however, is not a feature of the changes seen in biliary atresia.

In several cases of cytomegalic inclusion disease, nonspecific increase or decrease in bony density has been reported but cortical hyperostosis was not an associated finding.[1]

Hypervitaminosis A may produce roentgenographic changes similar to those of ICH[8] but can be readily excluded in the present case on clinical grounds.

The periosteal new bone formation observed in ICH may be similar to that seen in congenital syphilis,[6] but in the latter disease bone and soft tissue involvement would be expected to occur in a far more generalized fashion. The negative serologic tests of the mother and the patient would tend to rule out this possibility in the present case. Rubella can be similarly excluded.

Summary

In a newborn female infant with roentgenographic changes characteristic of infantile cortical hyperostosis prolonged obstructive jaundice developed due to giant cell hepatitis. The association of these two diseases, both of unknown cause but possibly viral in origin, has not been reported previously.

REFERENCES

1. Allen, J. H., Jr., and Riley, H. D., Jr.: Generalized cytomegalic inclusion disease, with emphasis on roentgen diagnosis, Radiology, 71:257-262, Aug. 1958.

2. Aterman, K.: Neonatal hepatitis and its relation to viral hepatitis of mother—a review of the problem, Amer. J. Dis. Child, 105:395-416, Apr. 1963.

3. Barba, W. P. II, and Freriks, D. J.: The familial occurrence of infantile cortical hyperostosis in utero, J. Pediat., 42:141-150, Feb. 1953.

4. Bennett, H. S., and Nelson, T. R.: Prenatal cortical hyperostosis, Brit. J. Radiol., 26:47-49, Jan. 1953.

5. Brenner, G., and Allen, R. P.: Skeletal changes in erythroblastosis foetalis, Radiology, 80:427-429, Mar. 1963.

6. Caffey, J.: Syphilis of the skeleton in early infancy; the non-specificity of many of the roentgenographic changes, Amer. J. Roent., 42:637-654, Nov. 1939.

7. Caffey, J.: Infantile cortical hyperostosis—a review of the clinical and radiographic features, Proc. Roy. Soc. Med., 50:347-354, May 1957.

8. Caffey, J.: Pediatric X-ray Diagnosis, 4th ed., Year Book Publishers, Chicago, 1961, pp. 1052-1056.
9. Caffey, J.: Personal Communication, 1967.
10. Clemett, A. R., and Williams, H. J.: The familial occurrence of infantile cortical hyperostosis, Radiology, 80:409-416, Mar. 1963.
11. Danks, D., and Bodian, M.: A genetic study of neonatal obstructive jaundice, Arch. Dis. Child, 38:378-387, Aug. 1963.
12. Garces, H., and Leiva, W.: Hepatitis infecciosa congenita en gemellos univitellinos, Rev. Chile Pediat., 25:427-435, Sept. 1954.
13. Hsia, D. Y. Y., Boggs, J. D., Driscoll, S. G., and Gellis, S.: Prolonged obstructive jaundice in infancy. V. The genetic components in neonatal hepatitis. Amer. J. Dis. Child, 95:485-491, May 1958.
14. Kitchin, I. D.: An atypical case of infantile cortical hyperostosis, J. Bone Joint Surg., 33B:248-250, May 1951.
15. Levin, E. J.: Congenital biliary atresia with skeletal abnormalities, Radiology, 67:714-722, Nov. 1956.
16. MacLeod, W., Douglas, D. M., and Mahaffy, R. G.: Infantile cortical hyperostosis, Clin. Radiol., 16:269-273, July 1965.
17. Neuhauser, E. B. D.: Personal communication, 1967.
18. Potter, E. L.: Pathology of the Fetus and Infant, 2nd ed., Year Book Medical Publishers, Chicago, 1961, pp. 533-534.
19. Potter, E. L.: Personal communication, 1967.
20. Röske, G.: Eine eigenartige Knochenerkrankung im Säuglingsalter, Mschr. Kinderheilk, 47:385-400, 1930.
21. Shorter, R. G., Baggenstoss, A. H., and Logan, G. B.: Neonatal hepatitis, Amer. J. Dis. Child, 98:359-369, Sept. 1959.
22. Shorter, R. G., Logan, G. B., Bollman, J. L., and Baggenstoss, A. H.: Neonatal hepatitis, Proc. Mayo Clin., 36:148-157, Mar. 1961.
23. Stokes, J., Jr., Wolman, I. J., and Blanchard, M. C.: Viral hepatitis in the newborn: clinical features, epidemiology, and pathology, Amer. J. Dis. Child, 82:213-216, Aug. 1951.
24. Stokes, J. S., Jr., Berk, J. E., Malamut, L. L., Drake, M. E., Barondess, J. A., Bashe, W. J., Wolman, I. J., Farquhar, J. D., Bevan, B., Drummond, R. J., Maycock, W. d'A., Capps, R. B., and Bennett, A. M.: The carrier state in viral hepatitis, JAMA 154:1059-1065, Mar. 1954.
25. Wong, P. W., Burnstine, R. C., and Hsia, D. Y.: "Neonatal hepatitis" in twin pregnancy, Pediatrics, 36: 138-140, July 1965.

Gangrenous Spider Bite in Los Angeles County

(Apparently by Loxosceles Reclusa)

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In 1957 the *Loxosceles* spider was shown to cause gangrenous bites in man.[1] Since that time, physicians have reported bites with increasing frequency from the south central and southeastern portions of the country. Until December of 1966, no one had reported cases of *Loxosceles reclusa* bites in the western states. Then a case appeared in San Diego, California, in which there were typical signs of a necrotic spider bite.[7] The two species endemic in California and Arizona, *L. unicolor* and *L. arizonica,* are not known to harm man. Following is a report of another case in California, this one in Los Angeles County.

Report of a Case

A 49-year-old nursery maintenance man was examined at our clinic on complaint of chills and severe pain in the upper portion of the right arm. He said that he had been bitten there by a spider the day before while he was at work, in the South San Gabriel area of Los Angeles County. The spider had been in a shirt that he had left hanging in a garage near the nursery. He killed the spider and, as the bite was not painful, he forgot about the incident until midnight, when chills began.

On examination, the attending physician saw that the arm was swollen and red over an area four inches in diameter at the site of the bite. In



Figure 1.—Site of spider bite on outer surface of upper arm. The central vesicle has been incised. There is a surrounding zone of induration.

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Reprint requests to: 1132 No. Stoneman Avenue, Alhambra 91801.

the center of the lesion there was a vesicle and a dark and purpuric area (Figure 1). There were smaller vesicles at the periphery. The bite was thought to be from a common garden spider at the time and the physician incised the vesicle and applied a dressing. He gave the patient injections of penicillin and tetanus toxoid, and dispensed a packet of chlorpheneramine.

When the patient returned the following day with complaints of increasing arm pain, respiratory distress and sharp substernal pain, electrocardiogram and spirometry studies were done. Increased expiratory breath sounds were heard but abated on use of an aerosol bronchodilating agent (Medihaler-iso, Riker). The spirometry tracing confirmed the lessening of bronchospasm. Intramuscular injection of 8 mg of dexamethazone seemed to aid in the relief of symptoms in the chest. Electrocardiographic findings indicative of mild transient cardiac ischemia disappeared the following day. Leukocyte count and differential sedimentation rate and urinalysis were all within normal limits.

As the week progressed, the patient felt pain in the muscles of the right chest wall as well as in the affected arm. Grip in the right hand weakened. The arm now had an area of necrosis in the center of the bite, and some of the surrounding skin was loosening and peeling (Figure 2). Several vesicles had ruptured.

The Los Angeles County Public Health Department entomologist* was consulted as to the possibility that a *Loxosceles* spider might have caused the bite. After seeing the patient, he said that clinically the case certainly typified the descriptions of *Loxosceles* bites. He conducted a search of the nursery but found no specimens of the spider.

By letter the lesion was described to Dr. Frank Perlman of Portland, Oregon, an authority on spider bites. He said that the description fitted the lesions caused by the *Loxosceles reclusa,* and he mentioned the possibility of skin testing for sensitivity to the class *Arachnida* with spider extract, but an attempt to obtain spider venom for skin testing from various antigen supply houses was unfruitful.

When specifically asked whether the arthropod that bit him might have been a tick (for there is a pajaroello tick found in the Southern California area whose bite causes a similar but smaller necrotic lesion[5]), the patient said he was certain it was a spider. He returned for weekly inspection of the lesion for three months, when an eschar (Figure 3) formed and sloughed spontaneously. The cavity was debrided and sutured and healing followed. The pathologist's report on the debrided tissue described an area of fibrin, lymphocytic infiltration and multinucleated giant cells (Figure 4).

The patient returned to work and had no chronic pain or thoracic symptoms.

*William G. Waldron.

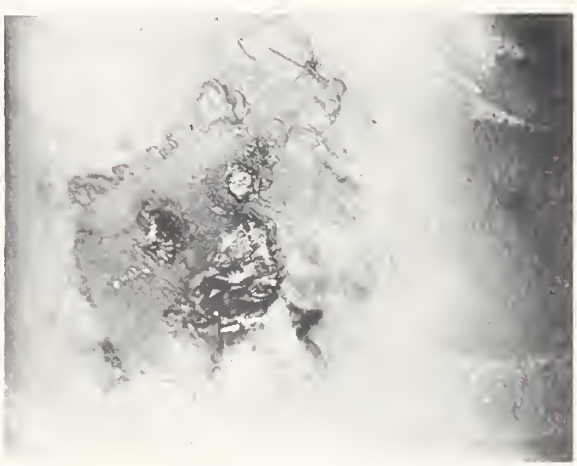


Figure 2.—Central necrosis, same lesion as in Figure 1, a week later. The vesicles have burst and the surrounding skin is beginning to peel.



Figure 3.—Two months after the bite an eschar, 2 inches by 4 inches, has formed.

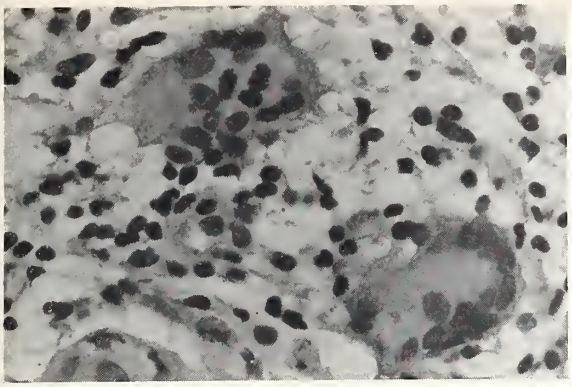


Figure 4.—Biopsy specimen, X600, showing fibrin, lymphocytic infiltration and multinucleated giant cells.



Figure 5.—Loxosceles reclusa spider, shown about twice normal size.

Discussion

The recluse spider, *Loxosceles reclusa,* is light brown and rather smooth. Its legs are proportionally long (Figure 5). The males are 3/8 inch long and 3/16 inch wide, the females slightly larger. A dark band shaped like a violin, which extends from the eyes back to the end of the cephalothorax, helps to identify the species.[3]

The bite of the recluse spider is only slightly painful at first. Later the area becomes swollen and tender and a vesicle appears, surrounded by an area of necrosis. Slow healing leads to an eschar formation which sloughs some weeks to months later and heals by scarring.[2] Animal experiments were done in 1957 which incriminate this species of *Loxosceles* with the necrotic bites. The venom is more toxic than that of the cobra, and is chiefly cytotoxic. As little as 0.5 mcg causes dermal necrosis in rabbits.[8] Other symptoms may be due to release of histamine rather than to direct action of the venom.[5] There is a rare type of loxoscelism associated with hemolysis, jaundice and hemoglobinuria which is now thought to be caused by a host factor.[9]

Treatment

Treatment in the present case with antihistamines and corticoids apparently did not shorten the course of the illness but did provide symptomatic relief. The aerosol bronchodilating agent also was helpful in relieving bronchospastic symptoms. That steroids do not prevent necrosis has been noted before, and experimentally this lack of effect has been found by Dillaha and coworkers[3] to be due to the lapse of time between the bite and the treatment.[3] The same investigators also expressed belief that steroids protect the patient from systemic effects of the venom. In an article in the Medical News section of JAMA, it was suggested that 80 mg of methylprednisolone be injected intramuscularly immediately after the bite, to be followed by the same amount every other day for the first week, then by reductions to 40 mg, 20 mg and 10 mg every other day for the next ten days.[8] It was also advised that for acute systemic reactions the patient be put into hospital and intravenous corticoids (initially a dose of 80 mg of methylprednisolone) be given.

In the present case the choice of debriding and closing rather than attempting skin grafting over the area worked well. Fast removal of the eschar, in some cases, helps speed eventual healing.[6] This may be due to removal of the cytotoxin still in the local site.

Summary

A 49-year-old nurseryman working in the San Gabriel area of Los Angeles County was bitten on the arm by a spider (which he killed). That night he had chills, bronchospasm and thoracic pain. Surrounding the site of the bite was a red, swollen area four inches across, with several vesicles at its center. Within a week, necrosis developed at the site of puncture. Treatment with antihistamines and corticoids relieved the symptoms but did not shorten the course. An eschar formed which sloughed three months later. Debridement and suturing were needed to close the cavity.

From the appearance of the lesion and the nature of the symptoms, the spider in this case is believed to have been *Loxosceles reclusa,* which until recently was unknown in the West.

REFERENCES

1. Atkins, J. A., Wingo, C. W., and Sodeman, W. A.: Probable cause of necrotic spider bite in the Midwest, Science, 126:73, 1957.

2. Atkins, J. A., Wingo, C. W., Sodeman, W. A., and Flynn, J. W.: Necrotic arachnidism, Amer. J. Trop. Med., 7:165-84, 1958.

3. Dillaha, C. J., Jansen, G. T., Honeycutt, W. M., and Hayden, C. R.: North American Loxoscelism, JAMA, 188:33-36, 1964.

4. Dooley, J. H.: Letters to the Editor, Calif. Med., 106:247, 1967.

5. Horen, W. P.: Arachnidism in the United States, JAMA, 185:839-43, 1963.

6. Lessenden, C. M., and Zimmer, L. K.: Brown spider bites, J. Kan. Med. Soc., 61:379-85, 1960.

7. Lewis, M. I., and Regan, J. F.: Necrotic arachnidism, Calif. Med., 105:457-62, 1966.

8. Medical News: Thirteen states report dangerous spider: "The Brown Recluse," JAMA, 200:19, 1967.

9. Riley, H. D., McLean, W. R., Start, A. H., Van Cleave, H. W., Garrison, G., Bryan, R. P., Nicholson, B. H., Sapper, H. V. L., and Nicholson, J. F.: Brown spider bite with severe hemolytic phenomena, J. Okla. St. Med. Assn., 57:218-23, 1964.

Hypothyroidism and Infectious Mononucleosis—An Unusual Association

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INFECTIOUS MONONUCLEOSIS is a generalized disease. Extensive biopsy and autopsy studies indicate there are as many lesions of infectious mononucleosis as there are organs and tissues in the body.[1,2,8] Although it is considered a rare complication, hypothyroidism has been known to follow acute and subacute thyroiditis. In 1961 Mosonyi and Rusvai[7] reported the findings in two patients in whom acute and subacute thyroiditis developed as a complication of infectious mononucleosis. Masked thyroiditis resulting in varying degrees of hypothyroidism may be a more frequent complication of this disease than is generally believed. It could in an occasional patient account for such frequently debilitating symptoms as general malaise, weakness and mental depression which may last for weeks, months and, in some cases, a year or more following an attack of acute infectious mononucleosis.

The purpose of this paper is to report a single case in which the relationship of hypothyroidism and infectious mononucleosis appears more than accidental. In this patient classical hypothyroidism, including myxedema heart, developed.

Report of a Case

A 29-year-old Caucasian male graduate student with no previous history of serious illnesses was seen in the Student Health Service in September 1964 with a history of fatigue, malaise and cervical adenopathy of three weeks' duration. A blood count revealed lymphocytosis with 14 per cent atypical lymphocytes. Heterophile agglutination was 1:1792 or greater. A diagnosis of infectious mononucleosis was made.

In October 1964, because of persistent symptoms, the patient was admitted to hospital. Serum creatinine was elevated to 1.5 mg per 100 ml with creatinine clearance of 90.8 ml per minute. There was no albumin or sugar in a 24-hour specimen of urine. No abnormalities were noted in liver studies. In an x-ray film of the chest, the heart size apeared to be within normal limits (Figure 1). Although there was little improvement, the patient was discharged after five days to convalesce at home.

In November 1964 he was readmitted to hospital because of continued fatigue and malaise and



Figure 1.—X-ray film, taken in October 1964, showing size of heart within normal limits.

From the University of California Center for the Health Sciences, Los Angeles.

Presented before the Minnesota Society of Internal Medicine, Minneapolis Veterans Hospital, Saturday, 20 May 1967.

Submitted 24 November 1967.

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new symptoms of muscle twitching, lateral chest pains, muscle stiffness, headache, nausea and questionable facial and submandibular puffiness and periorbital edema, mild chills and fever.

He appeared chronically ill and his complexion was sallow. There was slightly submandibular swelling.

The heterophile was 1:896. An x-ray film was considered unchanged. He was considered to be hypochondriacal and was treated with Librium® for the anxiety state and with multivitamins. After 14 days he was discharged with a diagnosis of chronic infectious mononucleosis.

In December 1964 he entered the hospital for the third time with nonspecific complaints of nausea, "black stool," aching in the lower abdomen and suprapubic area unrelated to meals, and persistent malaise.

As before, his complexion was sallow. Enlargement of a submandibular gland was noted.

Results of blood chemical determinations were within normal limits. An x-ray film of the chest showed a 2 cm increase in the transverse diameter of the heart in comparison with the previous film. This was attributed to failure to take a full inspiration. Hypomotility of the bowel was suggested in an upper gastrointestinal x-ray study. The patient was discharged after five days with a diagnosis of psychoneurosis manifested by asthenia and musculoskeletal symptoms.

Between January 1965 and June 1966 he was not seen by us, but a personal physician who saw him once during that time found him to be anemic and prescribed supplemental iron.

In July 1966, in a routine pre-employment physical examination, an enlarged cardiac silhouette was noted. The patient was referred to his personal physician, who confirmed the cardiac enlargement and suggested that there might be pericardial effusion. He was then referred to the Student Health Service for further evaluation and, on review of the x-ray film he brought with him (Figure 2), the finding of an enlarged flask-shaped heart was strongly suggestive of "myxedema heart," first reported by Zondek[10] and later classically described by Fahr.[3] Protein-bound iodine was 1.0 mcg per 100 ml of serum.

The patient was admitted to hospital for the fourth time with a diagnosis now of hypothyroidism and myxedema heart.

The symptoms and signs were classical for hypothyroidism—increasing dryness of skin, intolerance to cold, yellowness of skin, coarseness of hair, deepening of voice, facial puffiness, increased fatigability and mild shortness of breath, difficulty in completing studies, and tendency to be less physically active.



Figure 2.—Enlargement and "flask shape" of heart shown on film taken in July 1966.

Hemoglobin was 12.7 gm per 100 ml of blood, the mean corpuscular hemoglobin 33, mean corpuscular hemoglobin concentration 33 and mean corpuscular volume 102. Results of urinalysis were within normal limits. Serum carotene was 830 (normal 250) and serum cholesterol 305 mg per 100 ml. An electrocardiogram showed sinus bradycardia, low QRS voltage. Increased transverse diameter of the heart was noted on an x-ray film of the chest. Radioactive iodine uptake was 1.6 percent at six hours and 2.4 percent at 24 hours. The red corpuscle uptake of T_3 was 21 percent (normal 25-35 percent). PBI was 0.8 percent. A test for antithyroid antibodies was positive in a 1:10 dilution.

Thyroid replacement therapy was begun, and over the next three months the patient made dramatic recovery from the hypothyroid state, and the heart size returned to normal (Figure 3).

Discussion

The symptoms and signs in the case here reported closely parallel those of subacute thyroiditis, but clearly also those of chronic infectious mononucleosis. The fact that the patient had severe infectious mononucleosis with probable renal involvement made it difficult to diagnose the concurrent symptoms of subacute thyroiditis and the early symptoms and signs of hypothyroidism.[5]

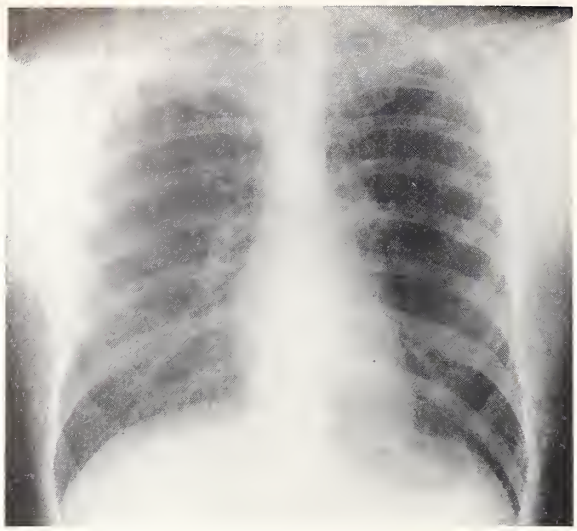


Figure 3.—Film taken after thyroid replacement therapy shows heart size back to normal.

Acute and subacute thyroiditis may be asymptomatic except for swelling and tenderness of the thyroid gland, although even this may be absent or so mild that it is overlooked. The onset of the disease may be insidious in nature, with the patient first noticing a "sore throat" and fatigability. These vague symptoms may last from two weeks on the average to as long as two to three months or more in 25 percent of the patients.[9] The classic symptoms include fever, a feeling of chilliness, generalized headache, night sweats, malaise, nausea, vomiting, cough, loss of weight and musculoskeletal pains. As can be seen, therefore, these symptoms may be also applicable for an upper respiratory infection as well as infectious mononucleosis. Mistaken diagnosis has been reported.[4,6] The variety of symptoms is related to the multiple organ involvement of infectious mononucleosis.

Thyroid involvement by infectious mononucleosis may be more frequent than is generally believed. Usually thyroiditis has a self-limiting course with no serious complications, and often is so mild that the diagnosis may be overlooked. The single case presented here seems to indicate a rather close relationship—more than an accidental association—between thyroid involvement and infectious mononucleosis. It is suggested that subacute thyroiditis or hypothyroidism be included in the differential diagnosis of a protracted course of infectious mononucleosis, for the symptoms of the former two diseases can be masked by the latter.

Summary

A patient with infectious mononucleosis had continuing symptoms several months after the acute phase of the disease. He appeared chronically ill, had a sallow complexion, easy fatigability, muscle twitching and stiffness, thoracic pain, headache, nausea, chills, fever and questionable facial and mandibular puffiness. He was thought to have chronic infectious mononucleosis and to be hypochondriacal.

A year and a half later, when cardiac enlargement noted on a routine examination led to further studies, hypothyroidism and "myxedema heart" were diagnosed. With thyroid replacement therapy the patient made dramatic recovery and the heart size returned to normal.

Generic and Trade Name of Drug

Chlordiazepoxide hydrochloride—*Librium*®

REFERENCES

1. Allen, F. H., Jr., and Kellner, A.: Infectious mononucleosis, an autopsy report, Amer. J. Path., 23:463-471, May 1947.

2. Custer, R. P., and Smith, E. B.: The pathology of infectious mononucleosis, Blood, 3:830, 1948.

3. Fahr, G.: Myxedema heart, JAMA, 84:345-349, 31 Jan. 1925.

4. Hoagland, R. J., Clinical manifestations of infectious mononucleosis, Amer. J. of Med. Sci., 240:21-29, 1960.

5. Isaacs, R.: Chronic infectious mononucleosis, Blood, 3:859, 1948.

6. Longcope, W. T.: Acute mononucleosis, Amer. J. Med. Sci., 144:781, 1922.

7. Mosonyi, V. L., and Rusvai, A.: Subacute Thyroiditis als Komplikation der Infektiosen Mononukleose, IV Inn Abt Arztl Fortbild. Inst. (Budapest). Z. Ges Inn Med., 16:18, 798-801, 1961.

8. Natvig, J. G.: Infectious mononucleosis with multiple organ involvement complicated by pseudomembranous laryngotracheitis: autopsy report, Acta. Path. Microbiol. Scand., 56:353-361, 1962.

9. Werner, S. C.: The Thyroid, 2nd Ed., Harper and Row Publishers, New York, 1956, pp. 829-837.

10. Zondek, H.: Das Myxodemherz, Munch. Med. Wschr., 65:1180, 1918.

A Role for Medicine in a New Era of Health Care

Part I

Fourth Progress Report of the Committee on the Role of Medicine in Society, California Medical Association

THIS REPORT OF THE Committee on the Role of Medicine in Society seeks to probe the nature and meaning of the new national purpose with respect to health and health care and to identify some of the determinants which will shape the changing role of the physician and medical practice in the years immediately ahead. The phenomenon of the national commitment to health and health care which came about in the 1960's will no doubt attract the attention of scholars in many disciplines for many years to come. The Committee, in an earlier report, "Prologue and Perspective,"* traced some of the events which preceded and evidently led to this national decision, but many questions remain unanswered with respect to why it occurred, why it occurred when it did, and why it took the form it did. Be this as it may, it is clear that a definite and largely irreversible step was taken by the 89th Congress. There were authoritative expressions of national purpose, and some laws with awesome potential for both good and ill were passed. The nation is now on its way toward something new in its approach to health care. The role of the physician and of the organized medical profession will change.

The National Purpose in Health Care

The national purpose in health care appears so far to be expressed mainly in generalities. Even the laws which are expected to achieve this purpose are notable for their broad permissiveness, general lack of specificity and emphasis on local initiative and local control. To the extent it has been spelled out, the definition of the commitment is found in statements such as the following:

- Health care is the right of every individual.
- There should be a personal physician for every person.
- Comprehensive health services are to be equally available to all.
- There should be mainstream medical care for all.
- Health and health care are a public responsibility.
- A pluralistic approach to providing health care involving both public and private sectors is to be tried.
- Local initiative and local control are to be emphasized.
- There is to be no interference with existing patterns of health care.

Statements such as these have received general public acceptance as goals to be achieved even though the specifics of the terms used, such as "health," "health care," "personal physician," "comprehensive health services," and "mainstream" are not spelled out, nor is the basic inconsistency between "public responsibility" and a "pluralistic approach" involving both the public and private sectors fully appreciated. The national purpose in health care is therefore in one sense diffuse and ill-defined while in another it is clear and unequivocal. It is the intent of society that the

*Committee on the Role of Medicine in Society, California Medical Association, "Role of Medicine in Society, Third Progress Report," April 1967.

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Committee on Role of Medicine in Society: Gerald Besson, Burt L. Davis, Sanford Feldman, Elmer F. Gooel, Sherman Mellinkoff, Malcolm C. Todd, and Malcolm S. M. Watts, chairman; and ex officio Carl E. Anderson, and Jean F. Crum

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specifics be defined to the extent that this is necessary, and that the goals be somehow achieved.

Infinite Scope of the National Commitment

The scope of this national commitment to health care is theoretically infinite. Medical science itself has no known boundaries, and research into its depths and ramifications reveals an expanding universe of opportunity for further scientific advances. Just as progress in medical science is theoretically infinite, so are improvements in the capabilities of health care services and so are the public expectations of better health. Thus as the population grows, as the capabilities of medical science and the effectiveness of health care services increase (and as longevity consequently increases) the demand for health services will further increase. The demands upon health care resources, including personnel, facilities and financing therefore also become theoretically infinite.

President Johnson's statement that all this will be "to the limits of this country's capacity to provide it"* recognizes that the infinite ideal cannot be achieved and that there will necessarily be limits or boundaries for each of these parameters. It is unlikely that any limits or boundaries will ever be rigidly fixed; rather it is likely they will continually change with changing medicine and a changing society. A role for the physician and for organized medicine in this vital process thus becomes essential.

Value Systems

Since it is clear that the infinite cannot be achieved in any aspect of health science or health care, the limits or boundaries will be determined by values of one sort or another. These will determine how far and in what direction medical science will develop, what practical limitations will be placed upon the broad humanitarian goals for health care services inherent in the national purpose, and how much of the nation's public and private resources in terms of personnel, educational and service facilities and dollars will be devoted to these purposes. Some value system or combination of value systems will necessarily be applied.

The pluralism which now characterizes American society embraces many different value systems which are often fundamentally at variance with one another. When a number of such value systems are applied to a single problem there is always a certain amount of incompatibility. Conflict and tension are likely to result. A number of such value systems pertain to the national purpose for health care. The Committee recognizes three as being of particular importance, and briefly identifies and discusses each one as follows:

A Value System for Science

There is a scientific value system which emphasizes truth and progress through careful observation and experiment. It values unproven theory only as a working hypothesis to be confirmed, modified or destroyed by new observations. It therefore holds that the pursuit of scientific knowledge—or social progress, for that matter—should be unfettered by any dogma or conceptual theory whether in research or education or in its application for better health and better living. This value system is supported by physicians, health scientists and the American people who have made available large sums of money for research in medical science.

A Humanitarian Value System

The humanitarian view or value system is rooted in the concept of human equality and emphasizes the equal entitlement of all to health and health care. It holds that society as well as the individual is responsible for personal health and that the benefits of medical progress should be readily available to all who need them without any significant ideologic, social, economic or political barrier. There is clearly great public support for this value.

An Economic Value System

There is also an economic value system which recognizes that health care resources will always be less than the demand for them and which therefore seeks to make the most efficient use of whatever personnel, facilities and financing can be made available. There is also great public support for this value.

Each of these value systems is pertinent to the national purpose in health care and each is to some degree incompatible and in conflict with the other two. Each has the ideologic support of the physician, who appreciates the value of medical science, who strives for the best possible care for all his

*President Johnson, 1965 Message to Congress "Advancing the Nation's Health."

patients, and who as a citizen and taxpayer is as concerned as anyone with high costs, inefficiency and waste of resources in health care. Each also has the ideologic support of the public and of society as a whole.

Value Systems and Advocacy

It is characteristic of American society that value systems develop advocates and that these advocates tend to become organized to a greater or lesser extent. They collect facts and informational material to support their advocacy and then proceed to use whatever ideologic, social, economic or political pressure they can to achieve their aims. This has been occurring with respect to value systems pertaining to health and health care. The dramatic success of the Manhattan Project in World War II suggested that, if similar massive support were given to research in health science, the knowledge necessary to overcome disease and illness would accumulate more rapidly. Advocates of this proposition were successful. Very considerable sums of money became available, medical research proliferated and thrived, and progress was spectacular. This drew public attention to health care and to the possibility of a broader application of humanitarian values to health. This humanitarian ideal is also deeply rooted in American culture and strong advocates readily appeared in support of this proposition. They became organized and used ideological, social, economic and political pressures which ultimately brought about the epochal health care legislation of the 89th Congress. More recently there has been growing concern with the cost of achieving this ideal level of health care for all, and strong advocates of the economic value system are now beginning to appear, particularly among labor and government purchasers or consumers of health care. It may be expected that they too will soon organize their advocacy, develop a body of knowledge, experience and information, and then exercise whatever ideologic, social, economic and political pressure they can bring to bear to lower or at least control the cost of health care. There is ample evidence that this has already begun to occur.

There are other ideologic and partisan value systems and advocacies at work in the field of health care. The Committee believes that those which have been described most directly pertain to the role of the physician and organized medicine.

The Decision Process and Public Opinion

The application of differing value systems to a single problem is certain to produce differing attitudes. The decision process must achieve some sort of balance or consensus within a complex of value systems and many other components of the traditional pluralistic American system. In health care it must in addition somehow deal with the basic inconsistency of a "pluralistic approach," involving both private and public sectors and a concept of "public responsibility."

The overall decision process is complex and hard to define. The component items may be difficult to identify or measure. For example, a man may use one value system when he needs the most sophisticated medical care for himself, and quite another when he is well and paying his insurance premiums or his taxes. Persons who are less closely involved with health problems may support one or another attitude as a matter of belief or principle. Those who are avowed advocates of the humanitarian approach emphasize equal entitlement of all to the very best health care and tend to be less concerned by its cost in dollars, while the avowed advocates of consumer interests tend to be more concerned with value received for a dollar spent. A health scientist, on the other hand, may hold the view that the current state of knowledge is not accurately reflected in the public expectations of immediate benefit from research and education, and in consequence may consider proposed or existing programs for providing health care services or for allocation of resources for any or all of these purposes to be inappropriate or even unjustified.

The opinions of individuals and of the more or less organized advocacies of differing attitudes or values are important but not in themselves decisive. Even the opinions and attitudes of legislators and other government officials are subject to a greater power: Public opinion is the ultimate force which in the long run determines the social, economic and political course to be followed. The decision process which results in a public attitude or opinion is therefore the crucial decision process in American society.

It is beyond the scope of this report to analyze the means by which public opinion is formed. Suffice it to say that public opinion at any given moment is something more than the algebraic sum of individual opinions and of the organized advocacies, although these are important. All these

opinions, advocacies, together with all the available facts and the possible alternatives, are somehow measured against those values or value systems which the public considers to be desirable or important at the given time. Just how this is accomplished is a subject of much speculation and comparatively little knowledge. But, however it may be arrived at, public opinion is the most powerful and decisive determinant of social, economic and political action in this nation, and it will decisively determine the future patterns of health care. It is essential that this fact be recognized by practicing physicians and by the organized medical profession.

A New Era in Health Care

A new era in health care was ushered in by the sweeping health legislation of the 89th Congress. It is an era in which public responsibility has to a considerable extent replaced traditional individual responsibility for health and health care. It is an era in which public opinion will to a substantial degree replace individual and even professional opinion in determining the directions and amount of support both for health care services and for the research and instruction in the health sciences which are so essential to their quality and quantity, and even to their distribution. Therefore, the important actions taken with respect to almost every aspect of health and health care will emanate from public opinion and public expectation.

The major factors or ingredients which will enter into the decision processes (which in turn will give rise to these actions) are to be found in the various statements describing the national purpose, in the implications of the infinite dimensions of the national commitment, and in the various systems of values and advocacies which were briefly discussed above. It is when these all interact with public opinion that attitudes are formed and decisions made which in the final analysis determine the direction and extent of what is done in both the public and the private sectors. This complex process is nebulous and diffuse and at times seems quite incomprehensible to a disciplined mind trained to think in terms of objectivity and precise measurements. Yet a decision or consensus is reached somehow, and somehow becomes implemented.

Paradoxically, this new era in health care—like its decision-making process—is both negative and positive at the same time. Its goals are diffuse and not easily quantifiable, its dimensions are infinite and therefore practically unreachable, and no one of its value systems can be fully realized except at the expense of not wholly realizing the others. Yet the attitude is positive. The intent is somehow to make progress. The quality, quantity and effectiveness of health care can surely be pushed and bullied nearer to the national goals. The dimensions, though infinite, can be more nearly approximated. And it is made quite clear that no one of the various values or value systems discussed earlier in this report is to be ignored. A pluralism of forces is therefore to be brought to bear with the hope and expectation that the resultant push will be a powerful one in the direction of better health and better health care.

It is noteworthy that while the concept of pluralism as a means to progress is not new, the incentives have changed in this new era of health care. The incentives of free competition and free enterprise have been largely replaced by a new incentive created by public opinion acting to stimulate both the public and the private sectors to find ways to satisfy their aims and aspirations. For better or worse, this may prove to be even stronger than the incentive of free enterprise.

The Committee believes that if the national purpose in health care is to be achieved in this new era, the many forces or ingredients involved must be applied or brought to bear in an appropriate fashion so that the resultant balance or mix will actually lead to "the betterment of the public health." This will require close attention and careful assessment of each of the important components on a continuing basis, and a means or method by which necessary pressure or power can be exerted. The appropriate balance or mix can be achieved and maintained much as a juggler might use skill and strength—*measured power* might be a more apt expression—to keep a number of items in approximately equal play at all times, yet each always in its proper relationship to the others.

A New Approach for Medicine

A new era in health care necessitates a new approach for medicine if it wishes to preserve its position and to influence and guide future developments. Such a new approach should place the physician and his profession in a role which is natural and in keeping with his calling. It should take full advantage of medicine's expertise and experience in virtually every aspect of health care and it should merit and receive public and professional

support. It should be responsive to the aspirations, goals and values inherent in the national purpose, take full cognizance of the practical limitations involved and seek to minimize the barriers and restraints to good health care.

For a number of years the California Medical Association leadership has been groping to find an appropriate role for itself and for organized medicine. There has been a gradual evolution of policy. On 7 August 1965, the Council adopted the following statement which, while limiting itself to the "Medicare" law and its regulations, does in fact acknowledge a general responsibility to work actively toward improvement of health care programs:

> " . . . that the CMA consider diligently the impact of Public Law 89-97 on patient care in coming months and years; and when regulations are imposed which are not in keeping with sound medical practice, the Association will forcefully pursue corrective action, through regulatory changes and/or legislative modifications."

In the autumn of 1967 a fiscal crisis developed in California's "Medi-Cal" (Title XIX) program, and on 4 November, the Council found it necessary to adopt a "Statement of Principle on Medi-Cal" in order to implement its policy to "forcefully pursue corrective action." The Medi-Cal crisis occurred when it appeared that there were insufficient funds to carry out the program as intended and severe restrictions in permissible services were imposed by the administrators. The goals which had been established for the program, and with which medicine agreed, were thereby jeopardized; and each of the three previously discussed major value systems was challenged. Advocates of economic values were in this instance vociferous in their advocacy and appeared to have the capability to weaken or destroy the overall aims of the program and to override scientific and humanitarian values as well. The CMA "Statement of Principle on Medi-Cal" utilized the expertise and experience of medicine to give strong support to the aims of the program and its beleaguered scientific and humanitarian values and to criticize the economic allegations constructively. This posture favorably impressed both the public, as reflected in the reaction of the press, and also the Legislature, which promptly decided against hasty action.

The Committee suggests that this action of the Council may well be a harbinger of a new approach for medicine in the new era of health care. Implicit in it is a recognition that if progress is to result from an on-going contest among various forces and advocates of differing value systems, there must be some kind of power or force which can be applied flexibly to influence the course of events by giving advocacy and support to any of the goals or values which happen to be misunderstood, under attack, or simply in need of strengthening. Also implicit is an assumption that the expertise and experience of the physician and the medical profession in the technical, humanitarian and economic aspects of health care can become this necessary power or force. Skillfully developed and deployed, it can influence the course of events in such ways as to achieve and maintain a reasonable balance among a pluralism of contesting aims and values. A responsible, flexible and informed advocacy can be the means by which this is accomplished.

It is the thesis of this report that in this new attitude and in this advocacy is to be found the new approach for medicine which is being sought for this new era. In this role the physician and organized medicine will always be seeking positively to strengthen what is weak and to repair what is defective, whether it be in definition of the national purpose, in determination of the scope of the national commitment, or in application of scientific, humanitarian or economic values in health care.

This use of expertise and experience to strengthen what is weak and repair what is defective is a natural role for a physician. Such an informed advocacy by organized medicine should merit strong professional approval and considerable public support. Indeed, it should be recognized that the aims of medicine can be achieved only if there is public understanding and cooperation, exactly as in medical practice the treatment is carried out successfully only with the understanding and cooperation of the patient. Thus any advocacy of medicine is likely to be successful in the long run only if it has the support of public opinion, just as any advice from the physician is likely to be followed only if the patient believes it to be good advice.

(In the forthcoming Part II of this Report, the Committee will suggest a program for organized medicine through which these concepts may be given practical expression.)

California Medicine

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EDITORIAL

A Fine Program Well Presented

From first to last, the program and the presentation of the 97th Annual Session of the California Medical Association were a credit to the host, to the scientific sections, to the ten assisting agencies and societies that contributed to the "federated" meeting, to the Committee on Annual Scientific Assemblies of the Scientific Board, and to the association's administrative staff. Even the Weather Man, a sometimes cranky character in San Francisco, must be praised for his kindness on this occasion.

The general meetings, which were excellently conceived and staged with smooth professionalism, had overflow audiences. Six television programs and four film symposia drew big attendance, as did individual meetings of the various scientific sections. Guest speakers were of a stature to fetch the interest and respect of any audience of physicians anywhere.

Although the list of organizations and persons to whom this association is grateful is too long to be set down here, there is room at least to make particular mention of Dr. John B. Dillon, who as chairman of the Committee on Annual Scientific Assemblies had the prime responsibility for initiating and prosecuting a program that enhanced the reputation of the California Medical Association.

The Baby and the Bath Water

TWO YEARS AGO the baby was born. Its gestation had been turbulent and the delivery somewhat precipitous. It may also have been a little premature, but somehow it survived and quite soon appeared to thrive. Its given name is California Medical Assistance Program. Medi-Cal is its nickname. Early in life it became widely admired for what it was likely to become when it grew up. The gleam when the program was conceived was that it would make it possible for the needy and near needy in California to receive health care within the mainstream of medical practice. It would remove the financial barriers. Government medicine for those in economic need would be indistinguishable from private medicine for those not in economic need. This principle was accepted although it was known that it would be costly.

In the two years that have passed since its birth, the baby has grown rapidly and it now requires more nourishment than had been anticipated. In many ways it has become more demanding of and annoying to those responsible for its care. In short, the baby is now a problem and, as is usually the case where there are problem children, each member of the family has his own opinion as to who is to blame and what should be done about it.

As this is written Assemblyman Gordon Duffy has just released a Preliminary Report on Medi-Cal from the Assembly Committee on Public Health containing a number of proposals which, according

to the statement, are "aimed at making the present program as efficient and economical as possible until more lasting action is taken." This is a worthy purpose so long as the larger aims of the program are not sacrificed unnecessarily on the altar of this economie or political expediency.

Elsewhere in this issue the Committee on the Role of Medicine in Society of the CMA draws attention to certain values which the Committee believes should be brought suitably into play whenever such important decisions are made with respect to how much of what resources are to be used in health care. That report suggests that economic efficiency and cost control should always be tempered by scientific values and humanitarian considerations, and that whatever decision is reached should reflect a deliberate and measured interaction of all these values.

Medi-Cal is yet in its infancy. It has the potential of providing truly mainstream health care for the needy and near needy of California and of showing the rest of the nation how this can be done by taking full advantage of the capabilities inherent in the American pluralistic free enterprise system. If we do not believe in this traditional American system we might as well throw the baby out with the bath water and be done with it. It would not survive anyway. But if we do believe in the American system, we should help the Medi-Cal baby to solve its problems, grow up, gain experience, learn from this experience, and ultimately justify the gleam for a truly California solution that was originally in its father's eye.

Erythrocyte Enzyme Defects

WHEN THE CLINICAL investigator attempts to increase our understanding of the biochemical basis of a disease process, he is often frustrated by unavailability of the tissue which is primarily involved. He must depend upon indirect evidence of the metabolic defect such as the accumulation of metabolic products in the plasma or in the urine. Then he may attempt to deduce the biochemical nature of the disorder. If by this means some insight has been gained into the problem, it may be possible to demonstrate the defect in a single, precious piece of biopsy or autopsy material.

In contrast to other internal organs, the red blood cells are readily "biopsied" and thus it has been possible to approach metabolism of the erythrocyte directly on a scale that has never been possible with any other organ. Several research laboratories have systematically measured the activities of many enzymes in the red cells of patients with anemia.

This issue of CALIFORNIA MEDICINE contains an impressive review by Valentine of some of the extensive information of this kind which has been obtained. No less than 12 enzymatic defects leading to hemolytic disease have already been described, and one of these, glucose-6-P dehydrogenase deficiency, can be further separated into at least 17 subtypes. It is noteworthy that the impressive catalogue of enzyme defects which lead to hematologic disease represents the result of work of scarcely more than the past decade. Perhaps we may take some justifiable parochial pride in the fact that almost one-half of all of the enzyme defects which are now recognized to lead to hemolytic disease were first described in California in Valentine's laboratory.

Although Valentine has reviewed only the red cell enzyme defects which lead to hemolytic anemia, enzyme defects which produce important clinical effects in other parts of the body may also be reflected in the erythrocytes. Notable among these is galactosemia, in which red cells, in common with other body cells, lack galactose-1-phosphate uridyl transferase activity. Although this disease does not produce important hematologic abnormalities, it is most readily diagnosed by the study of erythrocytes. Acatalasemia, a disorder which may be associated with a peculiar form of oral gangrene, is also most readily diagnosed by examination of erythrocytes. Studies of orotic acid metabolism in peripheral blood erythrocytes were instrumental in uncovering the deficiencies in orotidylic decarboxylase and orotidylic pyrophosphorylase which characterize orotic aciduria.

The findings which are reviewed demonstrate how extraordinarily fruitful biochemical investigation can be in the study of human disease. It is likely that as techniques for safely obtaining tissue from other internal organs are improved, similar progress may be made in the biochemical basis of diseases affecting other organs. In addition, the study of erythrocytes will continue to prove useful in the investigation of disorders of other organ systems in which the red cell may serve as a convenient mirror of the defects found elsewhere.

Nerve Entrapment in the Upper Extremity

DOYLE AND CARROLL, in their instructive paper, "The Carpal Tunnel Syndrome," appearing in this issue of CALIFORNIA MEDICINE, have focused our attention upon a not too infrequent cause of pain and paresthesia in the hand with or without weakness of certain intrinsic muscles. While excellent descriptions of carpal tunnel syndrome are relatively numerous in the literature, it is good to be reminded from time to time of the existence of such a condition. However, if a patient with acroparesthesia is encountered and the classic signs of a carpal tunnel syndrome are absent, it is also well to realize that there are other regions in the upper extremity where nerve entrapment is possible. These areas should also be investigated at the time of the physical examination.

The emerging nerve roots of the brachial plexus may be subject to compression or irritation as they pass through the cervical foramina, with resulting pain and paresthesia projected into the hand in a manner similar to that seen in discogenic diseases. The prepuberal descent of the shoulder girdle places the trunks of the brachial plexus in a vulnerable position relative to the first rib. The presence of a cervical rib, either completely formed in bone or remaining fibrous in its anterior portion, may be just sufficient to produce symptoms. Pregnancy, with changes in the center of gravity of the body, increased size of the breasts, and the necessity for exaggerated retraction of the shoulders frequently results in acroparesthesia in the hands and may even cause muscular weakness. The brachial plexus is supported by fibrous bands as it lies under the pectoralis minor beneath the coracoid process, and the excessive "throwing out of the chest and pulling back of the shoulders" may be sufficient to cause some entrapment of the cords of the brachial plexus, with resulting pain and paresthesia.

Other areas of nerve entrapment at more distal levels in the extremity have been described in the literature. The median nerve proximal to the elbow may be traumatized by the presence of a supracondylar process. This supracondylar process is a constant finding in some animals and is occasionally present in man; in such cases the median nerve lies posterior to it and is angled around its distal edge when the elbow is flexed. This condition may produce similar symptoms. More distally, the median nerve enters the forearm between the two heads of the pronator teres and may be compressed or irritated when the arm is forcefully pronated.

The ulnar nerve may be involved as it passes behind the medial epicondyle of the elbow or as it passes between the two heads of the flexor carpi ulnaris. This muscle is usually covered by a relatively thick fascia and the ulnar nerve passes through an oval slit in the fascia. Powerful contraction of the muscle distorts this slit and compresses the nerve. At the wrist joint the ulnar nerve passes under the pisohamate ligament and the situation is similar to that of the median nerve as it passes beneath the transverse carpal ligament. Compression of the ulnar nerve here has been graced with the ponderous name *the syndrome de la Loge de Guyon.*

This short discussion of areas where nerves may be entrapped is in no way intended to detract from the excellent paper by Doyle and Carroll. It is, rather, an additional contribution, intended to remind the reader that carpal tunnel syndrome is only one possible cause of paresthesia in the hand. If the specific signs of carpal tunnel syndrome are absent or atypical, these other possibilities should be investigated as part of a complete examination.

A Time to Lead

MALCOLM C. TODD, M.D., *President, California Medical Association*

WE ARE HERE TODAY not to recount our past achievements but to provide true leadership in an era characterized by swiftly changing patterns of medical practice.

The participation of our county society presidents here today has special meaning for me. For they, along with the elected delegates of the California Medical Association, represent the essence of local leadership which is the foundation of all that our association has been or will be. In a rapidly changing political and social environment, one thing remains constant: the qualities which a people will seek out to find its leaders. The local leaders who have joined us here exemplify these qualities: knowledge, integrity and compassion.

I would be remiss if I did not take this opportunity to point to another physician who, for the past year, has been charged with the grave responsibility of leading this association. A man who has unselfishly devoted untold hours away from his family and practice to respond to the multiple challenges facing medicine during a particularly turbulent time — President John G. Morrison. We also honor his lovely wife, Mary Lou, who exemplifies the great contribution which our wives so generously make.

As I look about this auditorium, I am again struck by the fact that California medicine is rich in leaders—strong men whose scope of knowledge is vast enough to enable them to reach far beyond responsibilities to the individual patients they serve, men capable of responding to the larger health needs and problems of this state with bold, new constructive approaches to the delivery of health care.

And in my opinion that is the essential task facing this association today. We must translate individual leadership into a true leadership role for the California Medical Association. Truly, gentlemen, we have giants in this day.

It has been said that medicine is blessed with a great legacy—a vigorous present and a challenging future. But simply to recount our scientific victories of the past—aseptic surgery, smallpox, diphtheria and thyroid vaccine, penicillin and antibiotic therapy, poliomyelitis eradication, blood transfusions and blood blanks, radioisotopes, organ and tissue transplants—is not enough. Physicians can no longer cling to a distinguished record of scientific achievement. We also must act now to gain leadership in the larger arena of social and economic change. When we fail to exert this leadership, others who are less qualified do it for us.

Society changes, regardless of our actions. It is our job and our duty to bring our collective knowledge, understanding and energy to bear on this change, so that it may truly be in the best interests of patient care. An apt illustration of how society has changed regarding medical care is brought out by McGraw's thought-provoking book, *Ferment in Medicine*. It notes a dramatic change in the thinking of our society. When a person is seriously ill or injured, the cry is no longer, "Call the doctor," but rather, "Take him to the hospital." Now it is perfectly clear that a hospital is not capable of taking care of anyone. But this and other erroneous concepts are becoming increasingly imbedded in the minds of our people.

John Galsworthy once said, "If you don't think about the future, you can't have one." Therefore, we must *do* some thinking. We must project our planning and programming for a better and healthier California of tomorrow.

Where are some of the essential areas in which the leadership of 24,000 California physicians must be exerted?

Presented before the House of Delegates of the California Medical Association, 26 March 1968.

Reprint requests to: California Medical Association, 693 Sutter Street, San Francisco 94102.

Legislation

The passage of the dramatic health legislation of the 89th and 90th Congresses heralded a new era of medical practice. Like it or not, we are now living in a time when public responsibility is replacing our traditional individual responsibility for health care, because of political expediency.

In 1965 the California Legislature approved welfare legislation known as Medi-Cal. It was a promising effort to bring the same high quality of health care to our needy citizens as is available to others of the public. Today the Medi-Cal program is in trouble. AB 5 went into effect without proper preparation, with unrealistic fiscal projections, and with poorly defined administrative details. CMA still believes in the basic concepts behind Medi-Cal. Our task is now to take the lead in retaining the basic components of the program without overburdening it, and at the same time develop creative new approaches to solving fiscal and other problems which have arisen.

The CMA strongly advocates a prepayment insurance program for comprehensive health services as provided under the law for Title XIX recipients. We feel that the program could best be administered by Blue Shield with our peer review system, with monthly premiums paid by the state government, and a provision for co-insurance payment for those category II patients who are not truly indigent.

Further, in resolving these problems we must implement a proper functional definition between skilled nursing home services and custodial or residential care. We recognize that residential care constitutes a social problem, and it must necessarily be dealt with, but not from Medi-Cal funds.

Medicare

Medicare has helped many over-65 citizens, especially those with prolonged or catastrophic illnesses, and for this help we are grateful. But we knew it would cost the taxpayer too much money. We warned that it would be difficult to administer, and we knew it would be inflationary. In less than two years, time has proven that we were right.

Regional Medical Program (Public Law 89-239)

Public Law 89-239 is commonly known as the bill concerned with heart disease, cancer and stroke. California's Regional Medical Program has completed the planning-grant stage and is now entering the phase of securing operational grants under the law. Examples of postgraduate education programs include coronary care units, angiography tracings, video tape programs, cancer registries and computer analysis of electrocardiograms. Eventually this program will probably be merged into Comprehensive Health Planning. But, for the present, we must be vigilant that these programs do not become coercive, and that they do not propagate at the expense of smaller, non-urban communities.

Comprehensive Health Planning (Public Law 89-749 and 90-179)

The emergence of federally-financed comprehensive health planning represents a new approach which cuts across nearly all aspects of the provision of personal and environmental health care. While we would have wished that such a program had been initiated by the private sector rather than government, this legislation provides us with a vital opportunity for leadership. By involving ourselves in the local implementation of this program we can lead rather than be led, we can guide, rather than be directed, and we can improve our health care system according to the values we know to be paramount, rather than having bureaucratic programs developed for us.

Cooperation between physicians and government is insuring that this legislation will not disregard established patterns of personal medical care. In choosing involvement rather than withdrawal we can retain the freedom of the individual physician to make his own decisions, guide the way to more effective provision of health care and, at the same time, renew public confidence in medical leadership. Both the California Medical Association and the American Medical Association recognize that planning, organization and distribution of health facilities and services are a primary responsibility of organized medicine. Even though we may not approve of the philosophical basis for such legislation, it is indeed necessary that we become involved in the broad scope of planning for the proper utilization of public funds where need does exist.

Comprehensive Health Planning and the many other government health care programs now under way point to a need for closer and broader relationships between the providers of medical care, patients, and the government. I would suggest that an advisory committee on health care for Califor-

nians be established. Such an advisory board would be composed of persons of influence in the fields of medicine, education, hospital administration, business, labor, religion, social work, minority groups, communications media, law, voluntary health agencies and others. Working with state government, such a group could give long-range direction to the future of health care.

The Profession's Role in Quality Health Care

Should any of you feel that physicians have no part in defining, in setting standards, and in applying quality, you should have attended the National Health Forum's meeting in Los Angeles last week. Over 800 were in attendance including members of the United States Public Health Service and the Department of Health, Education and Welfare, social workers, labor leaders, representatives of the Veterans Administration, of voluntary health agencies and of the health insurance industry, and a few scattered practicing physicians who almost forcibly acquired invitations — all telling us what quality is and how it is to be obtained.

If any lesson can be learned from that conference, it is that the medical profession must not only continue to be responsible for monitoring the quality of care in hospitals, but to expand these efforts to the physician's office, laboratories, rehabilitation units and all institutions in which they provide services or supervise the activities of other members of the health care team.

Not only must they be concerned about the criteria for evaluating the services they perform, they must also begin to look at the outcomes.

To those of us in California who have been involved in the past several years in the work of our Committee on the Role of Medicine in Society, these discussions came as no surprise.

We had anticipated this development in our examination of the parameters and elements which we felt contributed to the definition of quality care, and also when applied might suggest some kind of index which could ultimately be developed to enable us to judge the quality of medical care. These parameters include competence, availability, motivation, effectiveness, efficiency, and satisfaction. The elements, of course, are first the patient, the physician, the health team, facilities and equipment, plans and programs, and financing.

The role and involvement of the consumer played an important part at this conference. I should like to point out that the increasing involvement of the consumer as exemplified by his participation in Regional Medical Programs and Comprehensive Health Planning further suggests that we must begin to take the initiative in involving the consumer in the assessment which I have just described, so that we will be able not only to demonstrate what we are doing, but also to benefit from the suggestions, experiences and expectations of the patient.

I would urge all county societies to study the third Progress Report of our "Role Committee," and together with representatives of the allied health professions start using these parameters and elements as a basis for their evaluation of the various factors contributing to the total spectrum inherent in quality assessment of health care.

Health Manpower

We must continue to give increasing attention to the health manpower problems facing California — through the Health Manpower Council and through special efforts such as our recent program directed at the maldistribution of manpower, which means shortages in rural areas of the state, and some depressed areas of our cities.

Of necessity the physician is the key figure of the health manpower team. Our affluent society is making demands greater than the sources of manpower can provide. In order for physicians to provide quality care, they must learn to utilize fully the health care team we now have and to look toward the development of other kinds of needed personnel. I suggest we give consideration immediately to the establishment of an action program for training of a new paramedical profession — a "physician's assistant" — under the guidance of medical society sponsorship. In addition, we must give leadership in the training and recruitment of additional nurses, Licensed Vocational Nurses, technicians, and all members of the health team. A state workshop on the definition, composition, and function of the health team would be most timely.

Emergency Medical Care

We must take the lead in revamping present systems so that the right care is available at the right time. CMA's newly established committee on Emergency Medical Care has a vital role to fill in this area. We must take the individual responsibility to insure that the profession does not abdicate

practice on weekends, on Wednesday afternoon, or after 5 p.m. We must be sure that coverage is available 24 hours a day, every day.

Drug Abuse

The CMA has developed working committees on the timely subject of the misuse of drugs and will give positive leadership in this regard. I would urge the establishment of additional courses in health education to the junior high and high school curricula to include drug abuse, narcotics, LSD and marijuana, the effects of alcoholism and cigarette smoking, sex education and personal health care.

Definition of Life and Death

Perhaps the traditional response by physicians and attorneys toward life and death needs reexamination and reevaluation. New techniques, procedures, and materials have added to the prolongation of life. The remarkable heart transplants have created new attitudes as a milestone, and a significant breakthrough was reached in December 1967. I propose the formation of a highly professional state commission of many disciplines to evaluate and assess the impact of organ and tissue transplants. This commission would make thorough studies of the ethical, legal, moral and technical implications of such advances, and develop guidelines for their application. Changes in consent laws will be necessary. Someone must make judgment on transplants and the definition of life and death, and this can only be the physician.

Professional Liability

As I have traveled about the state this year, malpractice insurance and professional liability is the subject of high priority among our physician members. Physicians are concerned, and they expect leadership from the CMA and county medical societies. We have reported on our survey and you are in receipt of the results of this malpractice study. We are working in liaison with the California Hospital Association and the California Bar Association. We have testified before the legislature. We have introduced legislation into the State Assembly that will assist members of our profession as well as the public. I urge you to support this currently pending legislation.

Further, I propose that a joint panel review board with the California State Bar be established immediately to assess cases with poor results to determine if there was malpractice or to judge the validity of a potential case.

The Young Physician

Our Committee on the Role of Medicine in Society is now engaged in a long-term study of attitudes of medical students, interns and residents, and young physicians. These young men have developed new concepts. We hope to bring these young men into our official family of the CMA. I am proposing an "apprentice" membership of students, interns and residents known as "SIR" membership. This will allow them to become an integral part of the association, and to participate in the medical society activities and in committee work of hospital medical staffs.

Medical Education

Medical education is probably the profession's greatest challenge. Medicine is a science continually changing, always reaching upward toward a world free from the fear of illness. But this can only be achieved by training young men and women to provide quality medical care — the best care possible for our people. The leaders of the CMA simply are not satisfied with the results of our medical education. We are not satisfied with the curricular results, and we believe that we must do better. We must come to grips with the problems of today and the future. We must voluntarily upgrade our own individual educational standards by postgraduate education. This can be done through the CMA program of Continuing Medical Education. If all physicians will do this voluntarily, there will be no need for compulsory relicensure as proposed in the report of the President's Commission on Health Manpower.

Reporting continuing education could be made a requirement of the hospital medical staff acceptance. I would urge our medical staff executive committees to give consideration to this means of obviating any need for compulsory reexamination.

American medicine is educating many celebrated scientists, researchers and academicians, but far too few physicians — doctors who take care of people when they become ill. The deans of our medical schools, and particularly their faculties, have one basic responsibility, and that is to train doctors to take care of people when they get sick. Research and academic interests are necessary, but the obligation of our medical schools is the production of new physicians.

In 1950 there were 78 medical schools in the United States, four of them in California. In 1967 we had 94 medical schools in the United States, eight in California. Nine new ones will be added in the nation by 1971. By the mid '70s we will be graduating 10,000 physicians each year compared with 7400 in 1966. The physician population stands at 306,000 with 210,000 in active practice. But this is not enough. We have our own "brain drain" in this country — the constant and progressive decrease in the ranks of practicing physicians as members of the profession are siphoned off into research, teaching, and administration. It is ironic that President Johnson and his administration have successfully aggravated the shortage of medical personnel — the National Institutes of Health take 10 percent of the new physicians into research and the Public Health Service takes many young doctors into that organization.

The Federal Government has allowed proliferation of federally financed research projects, so that the number of physicians in full-time practice has decreased at the rate of almost one percent a year. Naturally the question is asked, how can we correct some of these deficiencies in developing medical personnel and faculties? Medical education is unique because the required ratio of instructors to medical students is four or five times greater than is required for other professions. Then, our medical school laboratories are not utilized effectively. While they should be perhaps operated from 8 to 12 o'clock and 1 to 5 each day, they are utilized only two or three hours a day. Finally, consideration should be given to conducting classes eleven months of the year instead of eight or nine months.

Yes, our CMA has taken many significant actions, and it has developed a substantial number of creative programs which have earned for us a reputation of constructive leadership.

Physicians are a very sophisticated group — highly educated and justifiably proud of their individual ability and independent philosophies, but if we are to be successful in holding our own against opposing forces, unity of purpose is essential. Lack of concert may often bring out weakness and our downfall. But if we achieve a unified front, the crevices of weakness cannot divide us in our endeavors.

May I offer special recognition to members of the Woman's Auxiliary — our wives. Their promotion of health careers, health education, the "gems" program and many community health services activities is laudable.

I could go on and on enumerating CMA's concerns — environmental health, relationships with the clergy, mental health and retardation, occupational health, alcoholism, group practice, poverty programs, disaster medical care. Because medicine is a noble profession with a great legacy and a heritage that we should and will pass on. If we have weakness, and if we lack perfection, it is because the majority of us are busy just taking care of people when they get sick, and do not have time to become professional politicians and protect our own interest. So I trust that my remarks on this occasion are such that I have been able to project the true image that "doctors are people who care."

With the help of the members of this House, of the Council, of our commissions and committees, of our county society officers, of all of our doctors and our excellent staff, the CMA will move forward. Because it is truly a "Time to Lead."

CMA Election Results

Dr. Albert G. Miller of San Mateo was elected President-Elect of the California Medical Association by unanimous vote of the House of Degelates at the recent annual meeting in San Francisco, and Dr. Malcolm C. Todd, Long Beach, was installed as President. Dr. Todd succeeds Dr. John G. Morrison of San Leandro, who as Past President, remains a member of the Council for a one-year term.

At its organizational meeting after the House adjourned, the Council named Dr. Richard S. Wilbur of Palo Alto as its chairman and Dr. Harold Kay of Oakland as vice-chairman.

The new President-Elect, a member of the Council since 1963 and its chairman for the past year, has also served in the CMA House of Delegates since 1948 and is at present a delegate to the American Medical Association.

In other election results in the House of Delegates, Dr. William F. Quinn and Dr. Joseph F. Boyle, both of Los Angeles, were re-elected Speaker and Vice-Speaker of the House, respectively.

Newly elected Councilors were Doctors Morton M. Haskell, Long Beach, George C. Andersen, Hermosa Beach, and Frank A. Rogers, Whittier, all from the Fourth District; John T. Saidy, San Mateo, Seventh District, and Thomas Elmendorf, Willows, Eleventh District. Re-elected to the Council were Doctors Frank C. Melone, Second District, Lewis T. Bullock, Fourth District, and Albert G. Clark, Eighth District.



President-Elect Miller (left) and President Todd share anticipation for the future, which Dr. Todd, in an address to the House of Delegates, spoke of as "A Time to Lead." (See Page 319.)

Professional Liability Study

A Socio-Economic Report Conducted by the Bureau of Research and Planning, California Medical Association

In June, 1967, a study concerning many aspects of professional liability was conducted by the Bureau of Research and Planning in cooperation with the Medical Review and Advisory Committee of the California Medical Association. The sample included one out of every six physicians in private practice in the State. By the end of September, following two mailings to non-respondents, a total of 2,626 or 66.4 percent of the 3,953 physicians in the sample had replied. The results of the Study are based upon 2,512 useable responses.

This *Report* contains the highlights of the findings of the survey, as well as selected information and tables from the total study. Interested readers may receive copies of the complete study upon written request.

Highlights of Findings

1. Approximately one California physician in three is covered for malpractice by Nettleship, another 20 percent by American Mutual and 11 percent by Medical Protective of Fort Wayne. Smaller percentages are covered by Aetna, Farmers/Truckers and Lloyd's London. No other single carrier is of major significance in terms of the number of physicians covered.

2. Of all 2,512 respondents to the survey, just 29, or 1.2 percent, said that they carry no malpractice coverage. The largest single number (16) without coverage is in Los Angeles County.

3. Very few physicians have recently obtained new coverage with either Farmers/Truckers or Medical Protective of Fort Wayne. Of physicians who changed carriers within the past three years, slightly more than 55 percent discontinued coverage with these two carriers. The trend in new coverage appears to be to Nettleship and American Mutual and, to a lesser extent, to Aetna.

4. Primary reasons why physicians changed carriers were (a) because the carrier discontinued providing coverage, either to the respondent singly or on a general basis and (b) because the premium became high, relative to rates charged by other carriers.

5. Almost 93 percent of physicians have $100/300,000 or more in coverage. More than half of the respondents (52.4 percent) have $100/300,000 in coverage; two-fifths (40.4 percent) have more than that. Just 7 percent have less than $100/300,000 of coverage.

6. Only 2.3 percent of all respondents have policies which provide for a deductible.

7. There is no significant difference between premium rates charged to physicians who are board certified and to those who are not.

8. Except in surgical fields, there is no difference in average premiums paid by physicians according to their ages.

9. Approximately one physician in five has umbrella type coverage; an above-average proportion of those covered by Aetna and Lloyd's have umbrella policies.

10. Fewer than one respondent in ten said that his broker or carrier requires that all insurance be placed through him. There was some confusion among respondents, however, as to what is meant by "all coverage."

11. About one in thirty respondents (3.5 percent) specified problems which they had experienced in securing malpractice coverage during the past three years. Main causes of problems were prior lawsuit or type of practice in which respondents engage. Of those who had problems, only one in seven currently has no insurance coverage.

12. Slightly more respondents think rates are excessive than think they are reasonable (45 percent vs. 41 percent). Anesthesiologists, most surgeons and G.P.'s more often think they are excessive. Opinion correlates strongly with premium rate, regardless of its justification based on risk, losses, etc.

13. High percents of respondents with Farmers/Truckers, Lloyd's and Nettleship think rates are excessive. Relatively more physicians covered by American Mutual think they are reasonable.

Study financed by the California Medical Association.
Reprint requests to: 693 Sutter Street, San Francisco 94102.

14. Respondents in Orange and Los Angeles Counties are likely to consider premiums excessive, while those in the Bay Area, Santa Clara County, Ventura County and Fresno County generally find rates reasonable.

15. Younger physicians tend to think rates are excessive; older physicians more often consider them reasonable.

16. Most respondents think that the service given by brokers or carriers is adequate. Criticism about service often is associated with criticism about premium rates.

17. Only 8 percent of respondents think that amount and types of coverage offered are insufficient .

18. The *single* comment most often made was that the CMA should provide malpractice coverage (3.9 percent of all respondents, 10.2 percent of anesthesiologists made this suggestion). Physicians covered by Farmers/Truckers often expressed this desire.

19. The primary reason for dissatisfaction among respondents who are *most* dissatisfied with all aspects of the malpractice situation is the high premiums.

20. Few respondents indicated any interest in additional group life insurance, many in group major medical insurance. Most respondents who expressed an opinion on the subject think that CMA should offer Workmen's Compensation coverage for physicians' employees.

Table 1a contains information as to percents of respondents, by geographic area and for the state, who are covered by each of the major malpractice insurance carriers who write policies in California.

Statewide, just under one-third of all physicians are covered by the Nettleship Company and another one-fifth by American Mutual. Among other carriers, the Medical Protective of Fort Wayne covers 10.8 percent of physicians, Farmers/Truckers, 4.3 percent and Aetna, 4.6 percent. Approximately one-sixth of all respondents are members of group practices. Since a majority of these respondents were insufficiently acquainted with their policies and/or were members of the Permanente Medical Group which is self-insured up to $25,000 and covered by Lloyd's London for amounts in excess, physicians in group practice are not shown by carrier, but rather retained in this separate category.

A small number of respondents, amounting to 1.4 percent of the total, have coverage under selected specialty societies. These, also, are grouped in all tables. As can be seen in the following table, the only specialty wherein coverage through a specialty society is of any significance is psychiatry.

Lastly, of all respondents, a total of 29, or 1.2 percent of the 2,512 who replied, stated that they do not currently have malpractice insurance. Detailed review of these questionnaires did not indicate that any such respondents were engaged in a type of practice wherein malpractice insurance would be unnecessary.

Table 1b shows percents of respondents in each medical specialty according to their malpractice carriers. Any preferences based on medical specialty can be observed by comparing percentages within specialties with the breakdown of all physicians according to carrier.

Physicians in medical specialties and most surgical specialties do not generally procure coverage through Farmers/Truckers. Conversely, anesthesiologists, pathologists and, to a lesser extent, radiologists tend to insure through Farmers. This may also be true in the fields of preventive medicine and neurology; however, total numbers of respondents in these specialties are insufficient for any conclusions to be drawn.

Percents of physicians in individual specialties who are covered by Aetna are either sufficiently close to the percent of *all* physicians covered by that company or based on an insufficient number of responses for any associations to be made. The one definite exception is the field of pediatrics, in which the percent of physicians covered by Aetna is extremely low.

Within the Lloyd's London group, there is an apparent preference by physicians in plastic surgery for the coverage which this company offers. Very few physicians outside of the surgical area or general practice are covered by Lloyd's.

Medical Protective of Fort Wayne provides coverage to physicians in most individual specialties at about the same rate as for all respondents. Two notable exceptions to this are the fields of pathology and psychiatry, wherein physicians appear to find policies offered by the company particularly acceptable. Below average numbers of physicians in orthopedic surgery and otolaryngology are covered by Medical Protective.

TABLE 1a.—*Malpractice Insurance Carriers Covering Respondents, by Geographic Area (Percent of Respondents)*[1]

Geographic Area	*Farmers/ Truckers*	*Aetna*	*Lloyd's*	*Medical Protective of Fort Wayne*	*Other Independent Commercial Carriers*	*Nettleship*	*American Mutual*	*All Specialty Societies*	*Respondent is member of Group Practice*	*All Others*	*Not Covered*
Metropolitan Areas:											
San Francisco-Oakland	1.6	0.4	3.3	14.2	4.9	0.4	56.2	3.5	14.6	0.2	0.8
San Jose	0.7	1.5	3.0	27.4	3.0	...	38.5	1.5	22.2	0.7	1.5
Sacramento	1.0	2.1	2.1	13.4	3.1	2.1	51.5	1.0	21.6	1.0	1.0
Stockton	3.0	3.0	...	9.1	6.1	3.0	69.7	...	6.1	...	...
Fresno	6.2	43.8	2.1	2.1	12.5	2.1	16.7	2.1	12.5	...	...
Los Angeles-Long Beach	4.8	0.2	1.6	6.6	3.8	64.1	0.2	0.7	15.8	0.3	1.7
San Diego	5.1	32.5	4.4	10.2	24.2	...	0.6	1.3	21.0	0.6	...
San Bernardino-Riverside-Ontario[2]	1.7	12.4	1.7	4.1	5.8	58.7	...	1.7	12.4	...	1.7
Bakersfield	6.9	3.4	3.4	3.4	...	58.6	...	...	20.7	...	3.4
Santa Barbara	...	3.3	...	23.3	...	46.7	...	...	20.0	3.3	3.3
Anaheim-Santa Ana-Garden Grove	7.9	6.5	...	17.3	2.2	51.8	...	1.4	12.2	...	0.7
Vallejo-Napa	7.7	...	...	23.1	3.8	...	34.6	...	30.8	...	...
Oxnard-Ventura	...	2.6	...	5.3	...	71.1	...	...	21.0	...	...
Monterey-Salinas	7.4	7.4	...	7.4	3.7	...	48.1	...	25.9	...	...
Non-Metropolitan Areas:											
Northern Coast	38.9	...	...	...	5.6	...	44.4	...	5.6	...	5.6
North-Central Coast	12.5	...	...	33.3	4.2	...	33.3	...	16.7	...	...
South-Central Coast	2.9	...	...	29.4	5.9	23.5	8.8	...	29.4	...	...
Sacramento Valley	23.1	3.8	...	...	3.8	3.8	53.8	3.8	7.7	...	...
North San Joaquin Valley	12.5	4.2	4.2	8.3	16.7	...	29.2	...	25.0	...	...
South San Joaquin Valley	3.8	...	...	...	7.7	53.8	11.5	...	23.1	...	...
Sierras	3.4	13.8	6.9	...	10.3	...	55.2	...	10.3	...	...
Total	4.3	4.6	2.1	10.8	5.6	33.1	20.2	1.4	16.5	0.3	1.2

[1] Percentages shown in all tables were rounded and may not add to 100; figures add to totals horizontally.
[2] Also includes Imperial County.

TABLE 1b.—*Malpractice Insurance Carriers Covering Respondents by Primary Medical Specialty (Percent of Respondents)*[1]

Primary Specialty	*Farmers/ Truckers*	*Aetna*	*Lloyd's*	*Medical Protective of Fort Wayne*	*Other Independent Commercial Carriers*	*Nettleship*	*American Mutual*	*All Specialty Societies*	*Group Practice*	*All Other*	*Not Covered*
Dermatology	...	10.2	1.7	16.9	1.7	23.7	33.9	...	11.9	...	...
Internal Medicine	2.0	5.0	0.3	9.2	4.7	36.3	22.1	0.3	19.8	0.3	...
Pediatrics	...	0.7	4.4	11.8	5.1	27.9	20.6	...	29.4	...	...
All Medicine	1.3	4.5	1.4	10.7	4.5	32.9	23.0	0.2	21.3	0.2	...
General Surgery	4.6	4.2	2.9	13.0	4.6	32.4	20.6	...	16.4	...	1.3
Colon and Rectal Surgery	...	14.3	...	...	14.3	42.9	14.3	...	14.3	...	...
Neurosurgery	...	4.0	4.0	...	8.0	20.0	48.0	...	16.0	...	...
Obstetrics-Gynecology	1.8	4.2	0.6	15.7	3.6	34.3	23.5	...	15.1	0.6	0.6
Ophthalmology	0.8	3.4	3.4	17.6	2.5	41.2	16.0	0.8	12.6	...	1.7
Orthopedics	7.8	3.9	2.9	3.9	4.9	24.3	26.2	...	25.2	1.0	...
Otolaryngology	1.7	5.0	3.3	3.3	1.7	45.0	26.7	...	13.3	...	...
Plastic Surgery	...	...	27.8	5.6	16.7	27.8	16.7	...	...	...	5.6
Thoracic Surgery	...	6.7	...	13.3	...	26.7	33.3	...	20.0	...	...
Urology	...	8.0	...	8.0	8.0	40.0	20.0	...	14.0	...	2.0
All Surgical	3.0	4.4	2.9	11.4	4.5	34.0	22.6	0.1	16.0	0.2	1.0
Anesthesiology	17.5	4.8	...	9.5	2.4	27.8	18.3	...	19.0	...	0.8
Pathology	16.7	4.8	...	21.4	2.4	16.7	9.5	...	26.2	...	2.4
Radiology	7.1	7.1	...	3.6	3.6	19.0	22.6	...	36.9	...	...
Psychiatry	0.7	0.7	...	21.8	2.3	30.1	9.8	24.8	3.8	0.7	5.3
Preventive Medicine	14.3	...	...	...	...	57.1	...	...	28.6	...	...
Neurology	8.3	8.3	8.3	...	8.3	16.7	25.0	...	25.0	...	...
Physical Medicine and Rehabilitation	...	...	...	12.5	12.5	25.0	...	...	50.0	...	...
Other Specialty not recognized	...	9.1	...	9.1	18.2	9.1	18.2	...	18.2	...	18.2
All "Other"	9.0	4.0	0.2	13.0	3.3	25.3	15.1	7.8	19.4	0.2	2.6
General Practice	5.3	5.3	2.7	9.1	8.9	36.6	18.3	0.1	11.7	0.5	1.4
Total	4.3	4.6	2.1	10.8	5.6	33.1	20.2	1.4	16.5	0.3	1.2

[1] Percentages shown in all tables were rounded and may not add to 100; figures add to totals horizontally.

Nettleship is an equally important factor in almost all specialties. An exception to this is in the specialty of pathology, where carriers such as Farmers and Medical Protective appear to be preferred. Figures indicate that in areas where Nettleship operates, it covers the vast majority of physicians in both ophthalmology and otolaryngology.

The coverage picture presented by American Mutual is similar to that of Nettleship, a strong position in most individual specialties. Relatively few psychiatrists or pathologists, however, are covered by American Mutual.

Among physicians covered under plans provided along with membership in specialty societies, the only group of any relative importance in the area of malpractice insurance is among psychiatrists, wherein almost one out of four respondents indicated coverage through their specialty society.

Table 2 contains information as to sizes of malpractice insurance policies which physicians have, according to medical specialty and for all physicians. Responses indicate the closest approximation of amounts and not necessarily the exact amount. The highest category contains all policies which are above the $100/300,000 level and the lowest category contains all which are below that amount.

Within all specialties, more than half of all respondents (52.4 percent) have policies in the area of $100/300,000 and another two-fifths (40.4 percent) have policies which are larger. Relatively insignificant numbers of physicians have smaller policies; the total of all those policies with limits below $100/300,000 amounts to just 7.2 percent of the entire group of respondents.

Policy sizes tend to be larger among surgical specialists than physicians in medicine or general practice. Among other specialties, policy limits are generally higher in anesthesiology and radiology, lower in pathology. Over 60 percent of respondents in several surgical specialties have limits above $100/300,000; among these are thoracic surgery, orthopedic surgery and otolaryngology. More than 70 percent of respondents in neurosurgery and plastic surgery have such high limit policies.

Among psychiatrists, the standard amount of coverage is $100/300,000. However, many re-

TABLE 2.—*Amount of Malpractice Coverage Physicians[1] Carry, by Medical Specialty*
(Percents read horizontally)

Medical Specialty	Amount of Malpractice Coverage[2]					
	Under $100/300,000		$100/300,000		Over $100/300,000	
	Number	Percent	Number	Percent	Number	Percent
Dermatology	4	7.6	34	65.4	14	26.9
Internal Medicine	21	7.4	163	57.6	99	35.0
Pediatrics	2	2.1	57	59.4	37	38.5
General Surgery	6	3.0	83	42.6	106	54.4
Thoracic Surgery	0	...	4	33.3	8	66.7
Colon and Rectal Surgery	1	16.7	4	66.7	1	16.7
Urology	0	...	22	52.4	20	47.6
Neurological Surgery	0	...	6	28.6	15	71.4
Obstetrics-Gynecology	2	1.4	78	55.7	60	42.9
Ophthalmology	2	2.0	57	55.9	43	42.2
Orthopedic Surgery	0	...	27	36.5	47	63.5
Otolaryngology	3	5.7	15	28.8	34	65.4
Plastic Surgery	0	...	5	29.4	12	70.6
Anesthesiology	3	3.0	35	34.7	63	62.4
Pathology	0	...	19	63.3	11	36.7
Radiology	1	1.9	21	39.6	31	58.5
Psychiatry	36	29.8	74	61.2	11	9.1
Preventive Medicine	0	...	2	40.0	3	60.0
Neurology	2	22.2	3	33.3	4	44.4
Physical Medicine and Rehabilitation	0	...	3	75.0	1	25.0
Other Specialty—not recognized	0	...	3	42.9	4	57.1
General Practice	65	10.2	364	57.2	207	32.5
Total	148	7.2	1,079	52.4	831	40.4

[1]Excludes physicians in group practice.
[2]Closest approximation.

spondents in this specialty have smaller policies and few have larger policies. Almost 30 percent of psychiatrists have under $100/300,000 of coverage, compared with just 7.2 percent of all respondents.

Table 3 presents information concerning physicians who have malpractice insurance policies which contain a feature requiring payment of an initial deductible amount.

Among all respondents outside of group practice, just 2.3 percent reported the presence of a deductible feature in their policies. While relatively infrequent in all specialty groups, physicians in surgical specialties and in general practice appear somewhat more likely to have deductible features in their policies than do physicians in medical or "other" specialties.

Table 4 indicates premium amounts for standard policies paid by physicians in selected medical specialties, regardless of insurance carrier, as well as medians and interquartile ranges. Because averages were interpolated from grouped data, dollar amounts shown may vary slightly from the actual amount paid by the median physician in the range. It should be noted that sub-specialties, as applicable, are included with these major specialties. Excluded from this table are a few primary specialties for which there were insufficient numbers of responses to warrant their inclusion in tabular presentations.

Opinion expressed by California physicians about premium rates in each Standard Metropolitan Statistical Area and in non-metropolitan areas grouped geographically is shown in Table 5a. Opinions expressed according to their insurance carrier and their broad medical specialty grouping are shown in Table 5b.

There is only one area where more than three out of five respondents think rates are excessive: Anaheim-Garden Grove-Santa Ana; 62.6 percent of respondents in this area have this opinion about rates. It is also worthy of note that more than half of all respondents in the Los Angeles-Long Beach Metropolitan Area think that rates are excessive. Were those respondents who did not indicate an opinion to be excluded, the preponderance of "excessives" over "reasonables" in Los Angeles would be even greater. Physicians in the Bay Area, San Jose, San Bernardino-Riverside-Ontario, and the smaller metropolitan areas are more likely to consider rates reasonable.

The only type of malpractice insurance which was generally thought to be reasonable was that available through specialty societies. This, as seen in earlier tables, is most frequently coverage for psychiatrists. Slightly above average percentages of respondents covered by Aetna, Medical Protective and American Mutual think that rates are reasonable, while physicians covered by Farmers/Truckers, Lloyd's and Nettleship are more apt to think of them as excessive. An interesting note is that (in comparisons which appear in the complete study) average rates charged by Nettleship were generally lower than those charged by American Mutual; nevertheless, 52 percent of physicians covered by Nettleship think that rates are excessive and only 39 percent covered by American Mutual think so.

Physicians in surgical specialties and in anesthesiology are most likely to consider rates excessive. Three out of five respondents in anesthesiology expressed this opinion. An above average proportion of physicians in general practice also think that rates are excessive.

TABLE 3.—*Number and Percent of Respondents who have Malpractice Coverage which Contains a Deductible Feature,*[1] *by Major Specialty Group*[2]

Specialty Group	Total Respondents	Deductible Feature? Yes Number	Yes Percent	No Number	No Percent
Medicine	435	7	1.6	428	98.4
Surgery	664	18	2.7	646	97.3
General Practice	636	17	2.7	619	97.3
Other	330	5	1.5	325	98.5
Total	2,065	47	2.3	2,018	97.7

[1]Excludes respondents in group practice.
[2]See Table 1b for individual specialties contained in groups.

TABLE 4.—*Annual Premiums Paid for Malpractice Coverage Standard Policies, for Selected Medical Specialties (Excludes Respondents in Group Practice)*

Annual Premium	*Anesthesiology*	*Ortho. Surg.*	*Gen. Surg.*	*Int. Med.*	*GP*	*Dermatology*	*Pediatrics*	*Urology*	*Ob.-Gyn.*	*Ophthalmology*	*Otolaryngology*	*Radiology*	*Pathology*	*Psychiatry*
Under $100	...	...	...	1.4	0.8	...	...	...	...	...	...	...	...	3.5
$100-199	...	...	2.2	28.3	2.9	14.6	23.4	...	1.0	1.4	2.7	6.1	23.1	54.4
$200-299	...	...	0.7	42.0	5.5	4.9	40.3	...	1.9	20.5	10.8	18.2	30.8	32.5
$300-399	1.4	1.7	1.4	16.0	15.7	14.6	19.5	3.6	3.8	35.6	10.8	12.1	23.1	7.9
$400-499	2.7	3.4	4.3	5.5	17.1	29.3	7.8	10.7	11.4	15.1	13.5	9.1	3.8	...
$500-599	6.8	5.2	18.0	4.1	22.2	24.4	1.3	32.1	27.6	6.8	8.1	21.2	...	0.9
$600-699	13.7	15.5	20.1	1.4	17.5	7.3	5.2	28.6	23.8	6.8	21.6	15.2	3.8	0.9
$700-799	16.4	17.2	23.7	0.5	6.1	2.4	...	10.7	23.8	8.2	13.5	12.1	7.7	...
$800-899	13.7	27.6	14.4	...	3.7	2.4	1.3	10.7	5.7	2.7	2.7	3.0	7.7	...
$900-999	38.4	13.8	7.2	...	3.1	...	1.3	3.6	1.0	1.4	5.4	...	...	...
$1000-1499	6.8	12.1	4.3	...	3.3	...	...	...	...	1.4	8.1	3.0	...	...
$1500 and over	...	3.4	3.6	0.9	2.0	...	...	...	...	...	2.7	...	...	...
Total Response	73	58	139	219	509	41	77	28	105	73	37	33	26	114
Median	$860	$825	$715	$249	$510	$458	$267	$619	$620	$380	$625	$528	$293	$186
IQ Range	$608-$950	$699-$925	$592-$830	$184-$320	$401-$661	$350-$541	$206-$353	$538-$693	$527-$720	$311-$520	$420-$740	$325-$640	$212-$384	$140-$251

Among those physicians who generally think that rates are reasonable are those in medicine (52.3 percent), psychiatry (51.9 percent) and pathology (52.4 percent).

In general, the proportion of physicians who consider rates excessive correlates closely with dollar amounts paid for malpractice coverage. This may imply some lack of physician awareness of the differences which exist among medical specialties with respect to costs of malpractice coverage.

A total of 350 respondents, or 13.9 percent, made one or more comments about malpractice or a related topic in answer to an open-end question eliciting comments. Because of space limitations, the table showing such comments is not contained in this *Report*.

Anesthesiologists were more likely to make comments than were physicians in any other specialty; 26.8 percent of all anesthesiologists commented. Fifteen percent of anesthesiologists made comments about the medical profession, mostly that organized medicine should sponsor malpractice insurance; 11 percent had specific complaints about rates (this in addition to having checked "excessive" in a previous question concerning rates); 10 percent had other criticisms of malpractice carriers.

General practitioners and physicians in surgical specialties were about equally likely to have made some remarks; one in six G.P.'s and one in seven surgeons commented about malpractice or related subjects. General practitioners showed a relatively high degree of interest in having the medical profession offer malpractice coverage, while comments made by surgeons were more often about legislation, the legal profession or the public.

Few physicians in medical or "other" specialties made comments. The only single comment made with any consistency by respondents in medical fields was that they feel that they should be rated on an individual basis or with other physicians in medicine, rather than helping pay the costs for their peers in more hazardous specialties.

In order of frequency, the types of comments made most regularly were these (including 2 ties):

1. CMA or AMA should become a malpractice carrier or should use group pressure in dealing with carriers,

TABLE 5a.—*Opinion about Premium Rates, by Geographic Area*

Geographic Area	Total Respondents	Opinion About Premium Rate: Reasonable Number	Reasonable Percent	Excessive Number	Excessive Percent	No Opinion Number	No Opinion Percent
Metropolitan Areas:							
San Francisco-Oakland	514	247	48.1	182	35.4	85	16.5
San Jose	135	65	48.1	47	34.8	23	17.0
Sacramento	98	43	43.9	40	40.8	15	15.3
Stockton	33	12	36.4	13	39.4	8	24.2
Fresno	48	29	60.4	17	35.4	2	4.2
Los Angeles-Long Beach	936	325	34.7	476	50.9	135	14.4
San Diego	157	70	44.6	68	43.3	19	12.1
San Bernardino-Riverside-Ontario[1]	121	58	47.9	51	42.1	12	9.9
Bakersfield	29	14	48.3	13	44.8	2	6.9
Santa Barbara	30	11	36.7	13	43.3	6	20.0
Anaheim-Garden Grove-Santa Ana	139	41	29.5	87	62.6	11	7.9
Vallejo-Napa	26	12	46.2	10	38.5	4	15.4
Oxnard-Ventura	38	26	68.4	10	26.3	2	5.3
Monterey-Salinas	27	11	40.7	15	55.6	1	3.7
Non-Metropolitan Areas:							
Northern Coast	18	7	38.9	8	44.4	3	16.7
North Central Coast	24	13	54.2	8	33.3	3	12.5
South Central Coast	34	13	38.2	12	35.3	9	26.5
Sacramento Valley	26	11	42.3	13	50.0	2	7.7
North San Joaquin Valley	24	9	37.5	11	45.8	4	16.7
South San Joaquin Valley	26	11	42.3	12	46.2	3	11.5
Sierras	29	11	37.9	15	51.7	3	10.3
Total	2,512	1,039	41.4	1,121	44.6	352	14.0

[1]Also includes Imperial County.

TABLE 5b.—*Opinion Expressed by Respondents about Premium Rates, by Insurance Carrier and Medical Specialty Classification*

Variable	Total Respondents	Opinion About Premiums: Reasonable Number	Reasonable Percent	Excessive Number	Excessive Percent	No Opinion Number	No Opinion Percent
Insurance Carrier:							
Farmers/Truckers	108	39	36.1	61	56.5	8	7.4
Aetna	116	51	44.0	53	45.7	12	10.3
Medical Protective of Fort Wayne	272	120	44.1	116	42.6	36	13.2
Other Commercial Carriers	200	78	39.0	99	49.5	23	11.5
Nettleship	830	308	37.1	435	52.4	87	10.5
American Mutual	506	232	45.8	196	38.7	78	15.4
Specialty Societies	36	27	75.0	5	13.9	4	11.1
Medical Specialty Type:							
Medicine	553	289	52.3	170	30.7	94	17.0
Surgery	801	296	37.0	396	49.4	109	13.6
General Practice	735	269	36.6	379	51.6	87	11.8
Anesthesiology	126	41	32.5	75	59.5	10	7.9
Pathology	42	22	52.4	13	31.0	7	16.7
Radiology	84	41	48.8	26	31.0	17	20.2
Psychiatry	133	69	51.9	45	33.8	19	14.3
All Others	38	12	31.6	17	44.7	9	23.7

2. (Respondent) would rather be rated individually, or with members of own specialty, not in group,

3. Carrier is too willing to settle out of court rather than fight cases,

*4. Jury and/or courts unfair, awards too high, favor plaintiffs, or similar comment,

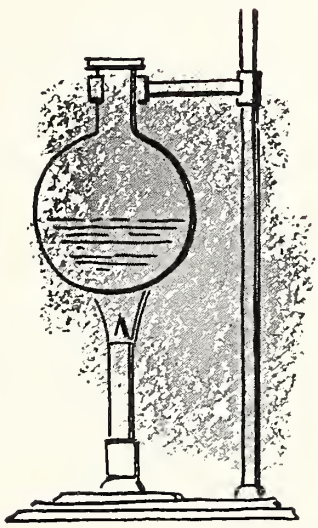
*4. Rates are increased periodically for no reason,

†5. Criticism of contingency basis of legal fees,

†5. Companies raise rates after suit, regardless of outcome,

6. Insurance carriers should never cancel out entirely.

*Tied for fourth in frequency.
†Tied for fifth in frequency.



18th Annual REDWOOD REGIONAL CONFERENCE

Konocti Harbor Inn
Clear Lake
Thursday Noon-Saturday Noon
May 2-4, 1968

Presented cooperatively by North Coast Counties Medical Societies, University of Southern California School of Medicine, Los Angeles, and California Medical Association Committee on Continuing Medical Education. A 12-hour course.

HOST: Humboldt-Del Norte County Medical Society
Regional Chairman: J. Roy Wittwer, M.D.

INSTITUTE FEE: $20.00. For additional information contact Continuing Medical Education office, California Medical Association, 693 Sutter Street, San Francisco 94102. All California Medical Association members and their families are cordially invited to attend.

GUEST SPEAKER: B. Marden Black, M.D., Professor of Surgery, Mayo Graduate School of Medicine, (University of Minnesota), Rochester, Minnesota.

PROGRAM THEME:

RECENT ADVANCES IN DIAGNOSIS AND THERAPY

THURSDAY, MAY 2

AFTERNOON SESSION

12:30—Introduction

12:45—Visual Medicine—David H. Blankenhorn, M.D., Fred L. Lieberman, M.D. and Phil R. Manning, M.D.

2:45—CONCURRENT WORKSHOPS

A. Symposium on Back Pain—Marvin H. Meyers, M.D. and A. Franklin Turner, M.D.

B. Neurology in General Medicine — John Eric Holmes, M.D.

C. Cardiac Arrhythmias—Michael Bilitch, M.D. and David H. Blankenhorn, M.D.

FRIDAY, MAY 3

MORNING SESSION

8:30—The Place of Surgery in 1968 in Thyroid Disease —B. Marden Black, M.D.

9:00—Cardiovascular Diagnosis—David H. Blankenhorn, M.D., Phil R. Manning, M.D., A. Franklin Turner, M.D. and Michael Bilitch, M.D.

10:15—CONCURRENT WORKSHOPS

A. Shoulder and Foot Pain—Marvin H. Meyers, M.D. and A. Franklin Turner, M.D.

B. Neurology in General Medicine — John Eric Holmes, M.D.

C. Cardiac Arrhythmias—Michael Bilitch, M.D. and David H. Blankenhorn, M.D.

AFTERNOON SESSION

1:30—Manifestations of Parathyroid Disease—B. Marden Black, M.D.

2:00—Newer Techniques in X-Ray Diagnosis—A. Franklin Turner, M.D.

2:45—CONCURRENT WORKSHOPS

A. Respiratory Disease — Chronic Restrictive and Obstructive Disease—Oscar J. Balchum, M.D.

B. Adverse Reaction to Common Drugs—Peter V. Lee, M.D.

C. Minor Surgical Procedures—Ernest H. Shore, M.D.

SATURDAY, MAY 4

MORNING SESSION

9:00—Office Approach to Chronic Pulmonary Disease—Oscar J. Balchum, M.D.

10:00—CONCURRENT WORKSHOPS

A. Pulmonary Function Studies — Oscar J. Balchum, M.D.

B. Newer Antibiotics—Peter V. Lee, M.D.

C. Minor Surgical Procedures—Ernest H. Shore, M.D.

18th annual regional postgraduate institute

AHWAHNEE HOTEL Yosemite Friday-Saturday May 10-11, 1968

SAN JOAQUIN VALLEY COUNTIES

Presented cooperatively by San Joaquin Valley Counties Medical Societies, Stanford University School of Medicine and California Medical Association Committee on Continuing Medical Education. A 12-hour course.

HOST: Fresno County Medical Society
Regional Chairman: Richard L. Jones, M.D.

INSTITUTE FEE: $20.00. For additional information contact Continuing Medical Education office, California Medical Association, 693 Sutter Street, San Francisco 94102. All California Medical Association members and their families are cordially invited to attend.

GUEST SPEAKER: Alfred J. Levi, M.B., Nuffield Visiting Fellow, Department of Medicine, Albert Einstein College of Medicine, New York.

PROGRAM THEMES:

INTERACTION OF DRUGS AND DRUG INCOMPATIBILITY . . . EVERYDAY PLASTIC SURGERY CORONARY ARTERY DISEASE

FRIDAY, MAY 10

Morning Session

9:00—**Practical Techniques in Plastic and Reconstructive Surgery**—Robert A. Chase, M.D.

10:15—**Drug Interactions: Their Implications for Drug Therapy**—Sumner M. Kalman, M.D.

11:15—**Diagnosis and Documentation of Coronary Heart Disease**—David A. Rytand, M.D.

Afternoon Session

2:30—PANEL DISCUSSIONS

A. Clinical Implications of Drug Metabolism — Sumner M. Kalman, M.D. and Alfred J. Levi, M.B.

B. Current Controversies in Management of Coronary Heart Disease — Donald C. Harrison, M.D., David A. Rytand, M.D. and Alfred E. Weisz, M.D.

C. Everyday Plastic Surgery — Robert A. Chase, M.D. and Donald R. Laub, M.D.

SATURDAY, MAY 11

Morning Session

9:00—**New Drugs in Cardiology**—Donald C. Harrison, M.D.

10:15—**Drugs and the Liver: Drug Metabolism in the Damaged Liver and Drug Induced Liver Damage** —Alfred J. Levi, M.B.

11:15—**Everyday Burn Care**—Donald R. Laub, M.D.

Afternoon Session

2:00—PANEL DISCUSSIONS

A. Clinical Implications of Drug Metabolism — Sumner M. Kalman, M.D. and Alfred J. Levi, M.B.

B. Current Controversies in Management of Coronary Heart Disease — Donald C. Harrison, M.D. and David Rytand, M.D.

C. Everyday Plastic Surgery — Robert A. Chase, M.D., Donald R. Laub, M.D. and Alfred E. Weisz, M.D.

In Memoriam

ABBOTT, KENNETH HARVEY, Los Angeles. Died 3 March 1968 in Glendale of myocardial infarction, aged 56. Graduate of the College of Medical Evangelists, 1936. Licensed in California in 1936. Doctor Abbott was a member of the Los Angeles County Medical Association.

✣

BELT, ROBERT LEROY, Glendale. Died 25 February 1968 in Pasadena of metastatic carcinoma, aged 68. Graduate of Rush Medical College, Chicago, Illinois, 1925. Licensed in California in 1925. Doctor Belt was a member of the Los Angeles County Medical Association.

✣

BEUTNER, KARL REINHARD, Vallejo. Died 19 February 1968 in Palo Alto, aged 48. Graduate of Hahnemann Medical College and Hospital of Philadelphia, Pennsylvania, 1944. Licensed in California in 1950. Doctor Beutner was a member of the Solano County Medical Society.

✣

DUNN, IRVING JAY, Los Angeles. Died 16 February 1968 in Los Angeles, aged 50. Graduate of Philadelphia College of Osteopathy, Philadelphia, Pennsylvania, 1944. Licensed in California in 1945. M.D. degree from California College of Medicine, 1962. Doctor Dunn was a member of the Los Angeles County Medical Association.

✣

EWING, FRED ELMER, Saratoga. Died 2 March 1968 in Saratoga of cerebral vascular accident, aged 87. Graduate of Rush Medical College, Chicago, Illinois, 1907. Licensed in California in 1924. Doctor Ewing was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

FERNISH, CHARLES A., San Jose. Died 9 February 1968 in San Jose, aged 72. Graduate of St. Louis University School of Medicine, Missouri, 1925. Licensed in California in 1926. Doctor Fernish was a member of the Santa Clara County Medical Society.

✣

FLETCHER, ELMER GORDON, Oakland. Died 4 March 1968 in Piedmont, aged 69. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1923. Licensed in California in 1927. Doctor Fletcher was a member of the Alameda-Contra Costa Medical Association.

✣

FRANCIS, VICTOR COLBOURNE, Long Beach. Died 24 November 1967 in Bellflower of carcinoma of the prostate and liver with metastes, aged 81. Graduate of the University of Toronto Faculty of Medicine, Ontario, Canada, 1909. Licensed in California in 1920. Doctor Francis was a member of the Los Angeles County Medical Association.

GREGORY, OSCAR L., Berkeley. Died 19 January 1968 in Oakland of cerebral artery thrombosis, aged 74. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1923. Licensed in California in 1940. Doctor Gregory was a member of the Alameda-Contra Costa Medical Association.

✣

HIEMSTRA, WYBREN, Beverly Hills. Died 15 February 1968 in Los Angeles of myelofibrosis with myeloid metaplasia, aged 67. Graduate of the University of Minnesota Medical School, Minneapolis, 1928. Licensed in California in 1938. Doctor Hiemstra was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

HILTON, JOSEPH J., Palos Verdes Estates. Died 17 February 1968 of arteriosclerotic heart disease, aged 78. Graduate of Northwestern University Medical School, Chicago, Illinois, 1913. Licensed in California in 1927. Doctor Hilton was a member of the Los Angeles County Medical Association.

✣

IRVINE, WENDELL C., Los Angeles. Died 23 February 1968 in Los Angeles of coronary occlusion, aged 59. Graduate of Columbia University College of Physicians and Surgeons, New York, New York, 1937. Licensed in California in 1941. Doctor Irvine was a member of the Los Angeles County Medical Association.

✣

MAGARIAN, SENNACHERIB M., Seal Beach. Died 20 February 1968 in Long Beach, aged 87. Graduate of Baltimore Medical College, Maryland, 1905. Licensed in California in 1926. Doctor Magarian was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

MCCOLL, JAMES M., San Diego. Died 12 February 1968 in San Diego, aged 82. Graduate of State University of New York at Buffalo, School of Medicine, Buffalo, 1910. Licensed in California in 1920. Doctor McColl was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

MEARNS, ROBERT B., Sacramento. Died 8 February 1968 in Sacramento of leukemia, aged 53. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1940. Licensed in California in 1948. Doctor Mearns was a member of the Sacramento County Medical Society.

MOCK, DAVID CLINTON, Redlands. Died 30 January 1968 in Redlands, aged 90. Graduate of the College of Physicians and Surgeons of Baltimore, Maryland, 1904. Licensed in California in 1914. Doctor Mock was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

NUSSENFELD, JOSEF H., San Francisco. Died 3 February 1968 in San Francisco of heart disease, aged 75. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1920. Licensed in California in 1938. Doctor Nussenfeld was a member of the San Francisco Medical Society.

✣

PETERS, JOHN RUSSELL, Glendale. Died 20 February 1968 in Glendale of arteriosclerotic cardiovascular disease, aged 71. Graduate of Ohio State University College of Medicine, Columbus, Ohio, 1928. Licensed in California in 1951. Doctor Peters was a member of the Los Angeles County Medical Association.

✣

PRESSMAN, JOEL JAY, Los Angeles. Died 26 February 1968 in Los Angeles of carcinoma of the colon, aged 67. Graduate of Harvard Medical School, Boston, Massachusetts, 1925. Licensed in California in 1927. Doctor Pressman was a member of the Los Angeles County Medical Association.

✣

ROGOZEN, ALEXANDER, San Jose. Died 8 February 1968 in San Jose of heart disease, aged 60. Graduate of the University of Louisville School of Medicine, Kentucky, 1935. Licensed in California in 1936. Doctor Rogozen was a member of the Santa Clara County Medical Society.

✣

ROUFF, ELLIOT ARNOLD, Los Angeles. Died 21 February 1968 in Los Angeles of lymphatic leukemia, aged 59. Graduate of the University of Michigan Medical School, Ann Arbor, 1931. Licensed in California in 1934. Doctor Rouff was a member of the Los Angeles County Medical Association.

✣

SMART, REGINALD H., Los Angeles. Died 7 February 1968 in Los Angeles of cancer, aged 64. Graduate of Rush Medical College, Chicago, Illinois, 1930. Licensed in California in 1931. Doctor Smart was a member of the Los Angeles County Medical Association.

✣

STEINBECK, FREDERICK E. O., Tarzana. Died 19 February 1968 in Tarzana of cerebral vascular accident, aged 66. Graduate of Medizinische Fakultät der Universität, Wein, Austria, 1925. Licensed in California in 1942. Doctor Steinbeck was a member of the Los Angeles County Medical Association.

✣

WELSH, WILLIAM WALLACE, Bishop. Died 20 February 1968 of heart disease, aged 58. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1934. Licensed in California in 1958. Doctor Welsh was a member of the Inyo-Mono County Medical Society.



WOMAN'S AUXILIARY
to the California Medical Association

What is WA-SAMA?

WHAT IS WA-SAMA? Well, to begin with the initials stand for Woman's Auxiliary to the Student American Medical Association. It was founded in 1957 in Philadelphia, with a two-fold purpose: To prepare its members for their future role as wives of physicians in the community where they will eventually live, and to bring wives and their families together with other medical families and medical groups for their mutual benefit.

The idea of WA-SAMA was very well met, as today there are approximately 6,000 members in 71 chapters, and each year more are joining; we have two new chapters this year in California. The National WA-SAMA is, for geographic feasibility, divided into seven regions and is active on the local, regional and national levels with programs designed for each level.

WA-SAMA works closely with WA-AMA (Woman's Auxiliary to the American Medical Association), the parent organization. A liaison officer is appointed by WA-AMA to WA-SAMA. She attends the WA-SAMA national convention and offers assistance through the year. In many states, California among them, a state liaison officer is appointed to work with the local chapters. As you know, being a physician's wife involves a great deal of responsibility and a young wife usually needs to adjust to the demands which will be made of her. Just as medical school, internship and residency is the training period for her husband, we feel that WA-SAMA is part of her training as his wife. We in California are trying to assist all our WA-SAMA chapters so that the wife of a student, intern or resident will be aware of the responsibilities that will be expected of her by her husband and by the community in which they will live when her husband becomes a full-fledged physician.

The WA-SAMA girls come from all over the United States and their chapters are as varied as their locations. Some groups are mostly social while others are highly organized in fund-raising and service projects. But they are alike in one respect — the beneficial services of WA-SAMA, which are:

1. *The information relay plan,* which sends the name of a girl moving to a new city to the WA-SAMA chapter in that area, or, if her husband is entering private practice, to the county medical auxiliary in the area. This way a girl always has a welcoming hand to help her in a strange city.
2. *A sharing of ideas* for solving common problems and hints on tried programs and projects. Subscriptions to the national publication *Chatterbox* keep members informed.
3. *The National Housing Information Service,* which now operates in over 30 cities, giving information on types of available housing, average rents, schools, pets, shopping, churches, distance from hospital and places of interest to their membership. More than 500 families were helped by this service last year.
4. *A programs and projects file* just filled with ideas to perk up a group's activities. Each chapter is asked to send a report on a program or project that has been successful to the National Coordinator so that others may benefit from their experience.

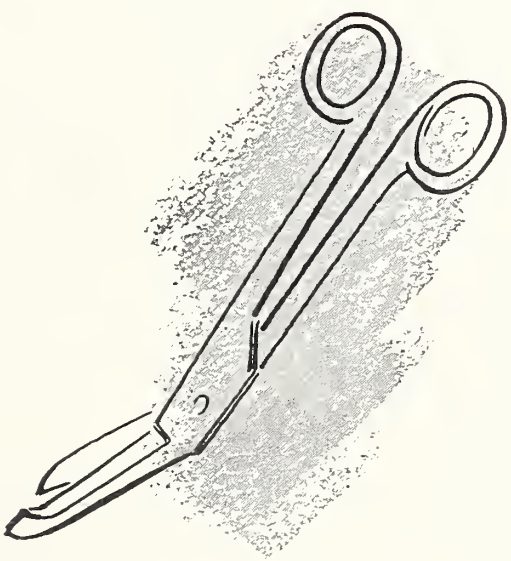
National dues are $1 per member per year. This $1 covers the cost of mailing *Chatterbox,* sending national mailings and covering chapter expenses at regional meetings, as well as all other WA-SAMA membership benefits.

WA-CMA (Woman's Auxiliary to the California Medical Association) now sponsors eight WA-SAMA chapters: The Long Beach Memorial Dames in Long Beach; U.C.L.A. and Los Angeles County Interns & Residents Wives in Los Angeles; U.C.I.-C.C.M. which over the next four years will be slowly moving from Los Angeles to Orange County; Loma Linda in Loma Linda; San Diego County Interns & Residents Wives; Orange County Interns & Residents Wives; and Bakersfield Interns & Residents Wives in Kern County. The Bakersfield Interns & Residents Wives and the Long Beach Memorial Dames are our two new chapters and we warmly welcome them to our WA-SAMA family. Each year, upon request, WA-CMA contributes an amount not to exceed $200 to each chapter for one delegate to attend their national convention, which this year is to be held at the Statler-Hilton Hotel in Detroit, April 23 to 27.

The counties that have WA-SAMA chapters appoint a county WA-SAMA chairman who works closely with the state chairman, the WA-SAMA regional vice-president for region seven and the chapter presidents. As experienced Auxiliary members, we try to be of assistance to these young wives in any way we can; and in turn, we have the privilege and pleasure of knowing these delightful, enthusiastic and intelligent girls who are helping support their husbands through medical school and raising young families.

How can you help? Well, this year a Sustaining Membership for friends of WA-SAMA has been adopted. A $5 annual Sustaining Membership will supplement the token dues and enable WA-SAMA to expand its many services to its 6000 members across the country. This membership can be obtained by contacting WA-SAMA National Headquarters, 2635 Flossmoor Road, Flossmoor, Illinois 60422.

MRS. JACK E. ENGELHARDT
State WA-SAMA Chairman



PUBLIC HEALTH REPORT

Hamlet C. Pulley, M.D., M.P.H.
Acting Director, State Department of Public Health

Drug Abuse—Now a Community Problem

DRUG ABUSE, especially among young people, has become a serious public health problem in California. The use of marijuana, hallucinogens and amphetamines by youths in all economic and social classes can be characterized as "epidemic." Standard approaches, which were developed to deal primarily with use of opium derivatives, and relying heavily upon penal sanctions, are not the answers to the new and growing drug abuse problem.

Here are some of the factors which make drug abuse a matter of concern to both the state and local public health departments and the medical community throughout California: (1) the inherent dangers to health resulting from misuse of drugs; (2) the extensiveness of the problem within the population, particularly the youth; (3) the "spreading" nature of recent drug abuse fads; (4) the reluctance of patients with illness directly or indirectly associated with drugs to seek medical care; (5) the hazardous practice of self-treatment or treatment by unqualified persons for problems associated with drug abuse; and (6) the association of drug abuse with certain communicable diseases, particularly hepatitis, venereal diseases, and tuberculosis.

There are serious problems connected with proper medical care for drug users. Many of the young patients who need medical attention boycott existing medical facilities either as a part of their rejection of "The Establishment," or out of mistrust and fear of prosecution for illegal traffic in drugs. Consequently, those cases which do come to physicians are likely to be severe, refractory or complicated and the patients themselves may have negative attitudes. In any event the most favorable time for treatment usually has passed by the time the patient comes under treatment.

Some private practitioners are confused about the legalities of treating drug users, and, believing some reporting system is entailed, prefer "not to become involved." Present state laws apply only to narcotics users, although some cities have local ordinances that require reporting of other drug users.

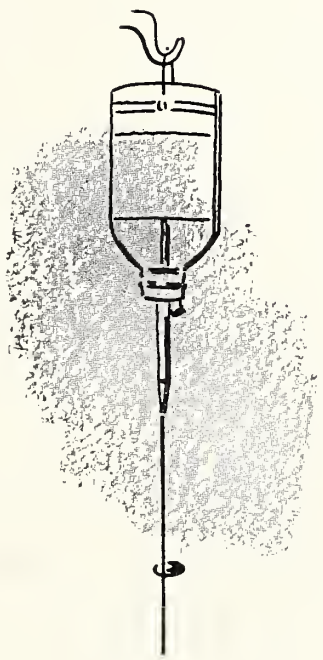
There may be a problem of paying for medical care, and existing "special" or "free" clinics may be insufficient to carry the load in areas of hippie colonies. Two such special clinics, established to meet the peculiar needs of the unorthodox groups are the Haight-Ashbury Medical Clinic in San Francisco, where about 100 private practitioners give volunteer services to patients who will not or cannot go elsewhere for help, and the Free Clinic in Los Angeles, where similar services are provided.

The need for medical care of a kind that will be accepted is particularly urgent, considering the large number of persons with medical problems associated with various forms of drug abuse. Treatment offered at present consists usually of little more than detoxification and does not provide for long-term follow-up and rehabilitation services. Early case finding is essential for best results of treatment. Lack of community treatment facilities for acute reactions associated with drug abuse has resulted in a dangerous pattern of self-treatment

which, in most instances, means that one form of drug abuse is merely added onto another.

We urgently need information for appropriate preventive approaches to the problem. This includes development and evaluation of improved health-oriented educational programs, for students as well as adults. Expanded efforts are also needed to measure the prevalence of drug abuse; to determine what groups are at high risk of becoming drug abusers; to discover the patterns of drug usage among high-risk groups—as well as within the entire population—and to determine the long-term effects of drug abuse.

Many agencies, public and private, have focused on the problem. However, their specific interests preclude a comprehensive approach, and result in extensive fragmentation of effort. The Department's primary responsibility is to assist in the mobilization of existing resources to find the nature, extent and causes of drug abuse, and then to draw together a comprehensive approach to the prevention, early detection and treatment.



NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Dr. Eliot Corday of Los Angeles was presented with the **Distinguished Fellowship Award** of the American College of Cardiology during the convocation ceremony of the 17th annual convention of the College. This is the third time in the history of the College that this award has been made. Dr. Corday was cited for "rare resourcefulness as a clinician, a teacher, an author and an administrator."

* * *

Dr. Austin B. Chinn has been appointed professor of medicine and director of the Research and Training Center in Rehabilitation, Dr. Roger O. Egeberg, dean of the University of Southern California School of Medicine, has announced. Dr. Chinn comes to USC from the U.S. Public Health Service, where he served five years as chief of the gerontology branch in the Chronic Disease Division.

ORANGE

The appointment of **Dr. Robert C. Combs** as associate dean for continuing medical education, UCI-College of Medicine, has been announced by Dean Warren L. Bostick. Dr. Combs formerly practiced in San Francisco where he was associate clinical professor of surgery at UC San Francisco Medical Center. He is a past president of the San Francisco Medical Society and of the California State Board of Medical Examiners. At UCI, Dr. Combs will hold concurrent appointments as clinical professor of Surgery at the College of Medicine and coordinator for **Orange County's Regional Medical Program.**

* * *

The third annual **postgraduate seminar,** presented by the **Childrens Hospital** of **Orange** County, **Orange,** will be held 21 and 22 June 1968, at the hospital facilities. Further information may be obtained from Dr. Merl J. Carson, Childrens Hospital of Orange County, 1109 W. La Veta, Orange, California 92668.

A NEW AUDIO-DIGEST SERVICE

The Audio-Digest Foundation, a non-profit subsidiary of the California Medical Association, is planning to add tapes of particular interest for Otorhinolaryngologists to its present group of subscription tape recordings, beginning on or about 1 September 1968. As with the other specialty programs, the ENT series will be issued twice each month, with each program one hour long. Editorial contents consist primarily of on-the-spot recordings from principal national specialty meetings, as well as condensations of recordings direct from postgraduate courses presented at leading teaching centers.

ENT specialists interested in becoming Charter Subscribers to the new service should indicate their intention by writing Audio-Digest Foundation, 619 S. Westlake Avenue, Los Angeles, California 90057, for order forms and information.

SAN DIEGO

A guest faculty from the National University of Ireland Medical School will be featured at the **San Diego Academy of General Practice** 1968 Annual Post-Graduate Symposium at Vacation Village in San Diego on May 11 to 12. Further information may be obtained from Dr. Thomas R. Early, President, San Diego Chapter, California Academy of General Practice, 3240 Main Street, Lemon Grove, California 92045.

SAN FRANCISCO

Dr. Robert M. Featherstone, professor and chairman of the Department of Pharmacology, School of Medicine, University of California San Francisco Medical Center, has been appointed consultant in pharmacology and toxicology to the National Institute of General Medical Sciences. Institute director Dr. Frederick L. Stone said that Dr. Featherstone will help develop a national program through research and training programs in pharmacology and toxicology.

* * *

The American Industrial Health Conference to be held at the Hilton Hotel in San Francisco, April 22 to 25, encompasses the annual meetings of the Industrial Medical Association and the American Association of Industrial Nurses.

YOLO

Appointments of six new members of the **School of Medicine faculty** at University of California, Davis, and the naming of Dr. Douglas D.

Vollan as **coordinator for Regional Medical Programs** (RMP) in heart disease, cancer, stroke, and related diseases were announced from the university recently.

Dean C. J. Tupper said that Dr. Vollan will assume responsibilities for RMP in the 23 Northern California and Nevada counties covered under a planning grant to Davis from the Division of Regional Medical Programs, National Institutes of Health. RMP is organized in California around the state's eight medical schools.

The faculty appointments were as follows:

• **Dr. Loring F. Chapman** — professor and chairman of the department of behavioral biology. Dr. Chapman comes to Davis from the National Institutes of Health where he was chief of the behavioral biology branch of the National Institute of Child Health and Human Development.

• **Dr. Louis W. Conway**, an associate professor of neurological surgery at the Medical College of Virginia, has been named assistant professor of neurosurgery at Davis.

• **Dr. Robert E. Smith**—assistant professor of physiology. Dr. Smith was at the University of Kentucky College of Medicine as assistant professor of physiology and biophysics.

• **Dr. G. Henry Schmitt**—assistant professor of pharmacology. He was an assistant professor of pharmacology at Kentucky.

• **Dr. Thomas L. Volk**, appointed assistant professor of pathology, was assistant professor in the department of pathology and oncology at the University of Kansas Medical Center in Kansas City.

• **Dr. Lois F. O'Grady**—instructor in internal medicine. Dr. O'Grady comes to Davis from the faculty of the University of Illinois College of Medicine. Besides teaching at Davis, she will be working with associate professor Dr. Jerry P. Lewis in studies of bone marrow recovery following radiation damage and bone marrow transplantation.



The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 66 of the Advertising Section.

ULTRASONICS IN OPHTHALMOLOGY—Diagnostic and Therapeutic Applications—Richard Earl Goldberg, M.D., and Lov K. Sarin, M.B., Wills Eye Hospital, Philadelphia. W. B. Saunders Company, Philadelphia, Pa. (19105), 1967. 223 pages, $24.00.

In an increasingly tense world, Goldberg and Sarin have managed to obtain the cooperation of German, Japanese, Australian, Finnish and American scholars. The subject of ultrasound is covered extensively in this text under three broad categories. First there are discussions of the history and basic physics of ultrasound. Then follow discourses on the specific techniques such as time-amplitude (A-mode) ultrasonography, intensity-modulated (B-scan) ultrasonography, and the Doppler transcutaneous flow indicator, along with chapters that explore problems in A-mode ultrasonography and the special transducers used in diagnostic procedures. The third group of chapters is devoted to applications of ultrasound in biometry, the therapeutic use of ultrasound, localization and extraction of intraocular foreign bodies, and the ultrasonic examination of arteries and veins. Finally there is an extensive bibliography of references to publications covering the field of ultrasonography.

This text is recommended to those interested in this newly developing field and as an excellent reference source.

R. M. SINSKEY, M.D.

* * *

CLINICAL HEMATOLOGY—Sixth Edition—Maxwell M. Wintrobe, M.D., Ph.D., D.Sc. (Hon., Manitoba), D.Sc. (Hon., Utah), Professor of Medicine and Director of Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah, College of Medicine, Salt Lake City, Utah; formerly Associate in Medicine, Johns Hopkins University, Associate Physician, Johns Hopkins Hospital, and Physician-in-Charge, Clinic for Nutritional, Gastro-Intestinal and Hemopoietic Disorders, Baltimore, Maryland. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. (19106), 1967. 1287 pages, $22.50.

Dr. Wintrobe has again accomplished the monumental task of bringing up to date his Clinical Hematology in the Sixth Edition, the First Edition of which appeared in 1942.

The general layout is similar to that of previous editions, but with chapters now on abnormal hemoglobin syndromes, bone marrow failure, and paraproteinemias. One still wonders why agranulocytosis and infectious mononucleosis occupy the same chapter, except for having a sore throat in common.

The book is very readable, and one is guided through electron microscope photographs, erythrocyte enzymology, new factors in blood coagulation, synthesis of hemoglobin, etc. Enlarged chapter outlines precede each chapter, as well as being in the table of contents, which may be helpful. References at the end of each chapter are extensive, chiefly prior to 1966.

The index seems inadequate, and smaller than before, despite the tremendous increase in material. With persistence, however, one can find what is known about anything of a hematologic nature. The book not having attained perfection, if you are hunting for Figure 20-20 as noted on page 614, you will find it on page 1148 instead of page 1159.

The author states in his preface, "As in the past, in preparing this book, I have had in mind the beginning student, the discerning technician, the advanced postgraduate, the practicing physician, the teacher, and even the bio-chemist and the sophisticated hematologist." This he has done.

This reviewer feels that this book is one of the medical classics and that it will continue to retain its position as the best textbook of hematology, despite the difficulties frequently encountered after so many editions.

WILLIAM F. LUTTGENS, M.D.

* * *

PATHOLOGY FOR THE SURGEON (BOYD'S)—8th Edition—William Anderson, M.B., Ch.B. (Edin.), Associate Professor of Pathology, University of Toronto; Surgical Pathologist, Toronto General Hospital; Consultant Pathologist, The Hospital for Sick Children; Consultant Pathologist, Women's College Hospital; Consultant Pathologist, The Queen Elizabeth Hospital. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1967. 842 pages, $18.50.

A textbook of pathology designed for surgeons seems desirable. This book blends Dr. Anderson's large experience at Toronto with some of the features that made Dr. Boyd's earlier versions entertaining and companionable.

The book is now an introduction and a junior encyclopedia. Major lesions and minutiae are discussed almost in the same breath, creating a sea of words often lacking in emphasis. Because a wide range of specialized material is presented, many chapters do not have authority, as witnessed in their outmoded bibliographies. Illustrations are numerous, but a number are handdrawn antiques, and many of the micrographs are muddy or unnecessary.

The major value of this book lies in its thoughtful and often amusing discussions of major problems in which the disciplines of diagnostic pathology and general surgery interact to determine the management of the lesion and the attached patient. This is the true business of this book, but much of the good is lost in verbiage devoted to aimless description and irrelevant conditions. It would have been better to restrict its range to make it a short and readable guide for the junior resident, since the specialist will read a book about his subject, not a chapter.

LLOYD SILVERMAN, M.D.

California Medicine

Abdominal Aortic Aneurysms

Unusual Clinical Manifestations

WESLEY S. MOORE, M.D., LESLIE PREGER, M.D., ALBERT D. HALL, M.D., AND FRANK E. MADDISON, M.D., *San Francisco*

■ *Misleading symptoms were responsible for failure to make the diagnosis of symptomatic abdominal aortic aneurysm in 15 patients. The presenting complaints appeared to be specific for other diseases, such as genitourinary disease, diverticulitis, intra-abdominal neoplasm and functional large intestinal disorders. A correct diagnosis was ultimately made in 12 patients and aneurysmectomy was performed. In three patients, who died of ruptured aneurysm, the diagnosis was not made until postmortem examination.*

An awareness of the atypical symptoms of aneurysms, careful physical examination and appropriate x-ray studies will lead to the diagnosis of symptomatic aortic aneurysms. Early resection will result in a lower mortality rate.

ABDOMINAL AORTIC ANEURYSMS are usually diagnosed by palpation of a pulsatile abdominal mass. Large aneurysms, or those which expand at a rapid rate, often produce symptoms. Standard textbooks have stated that as many as 40 percent of abdominal aortic aneurysms produce symptoms, including midabdominal discomfort, pain in the back or the sensation of a pulsatile abdominal mass.[1,6] That abdominal aortic aneurysms can also produce symptoms which mimic other diseases is not always mentioned or is frequently forgotten. When an aneurysm causes atypical symptoms the correct diagnosis may not be made and the aneurysm may rupture before the true significance of the symptoms is appreciated. This report reviews our experience with abdominal aortic aneurysms which presented in an unusual manner.

Materials and Methods

Two hundred consecutive cases of abdominal aortic aneurysm seen at the Veterans Administration Hospital, San Francisco, were reviewed. The presenting complaints, the diagnosis of the referring physician and the diagnosis made on admission were noted. The cases which had initially been misdiagnosed were selected for analysis. The diagnosis of abdominal aortic aneurysm was ultimately confirmed in all of these patients at operation or autopsy.

From the Departments of Surgery and Radiology, Veterans Administration Hospital and the University of California School of Medicine, San Francisco. Supported in part by USPHS Grants HE-32,432 and HE-11,128.

Submitted 1 February 1968.

Reprint requests to: Veterans Administration Hospital, Forty-Second Avenue and Clement Street, San Francisco 94121 (Dr. Hall).

Results

Fifteen of the 200 cases of symptomatic aortic aneurysm reviewed were misdiagnosed upon initial examination. The diseases most frequently mimicked fell into four categories: genitourinary disease, diverticulitis, intra-abdominal neoplasm and functional large bowel disorder. Correct diagnosis was made ultimately in 12 of the 15 cases and operation was carried out. In the other three cases the patients died of ruptured aneurysm and the correct diagnosis was not made until postmortem examination (Table 1). The following case histories are representative.

Case 1.—A 65-year-old man entered the hospital with a six-day history of left flank pain radiating to the groin and testes. The diagnosis made by the admitting physician was ureteral stone. A pulsatile abdominal mass was later found on physical examination. An intravenous pyelogram did not demonstrate a stone, but the left ureter was displaced laterally. After this examination it was decided that the abdominal aortic aneurysm was producing the pain and the aneurysm was resected. During surgical exploration it was found that the aneurysm was dissecting intramurally and that rupture was imminent. The patient made an uneventful recovery and was discharged free of symptoms.

TABLE 1.—*Diagnostic Accuracy in Abdominal Aortic Aneurysms*

Case No.	Diagnosis by Physicians: Referring	Admitting	Ward	Deaths
1	Genitourinary disease	X	C	—
2	Genitourinary disease	C	C	—
3	Genitourinary disease	C	C	—
4	Genitourinary disease	X	X†	Nonoperative
5	Genitourinary disease	X	C†	—
6	Genitourinary disease	X	X*†	—
7	Diverticulitis	X	C	Nonoperative
8	Diverticulitis	X	X*†	Nonoperative
9	Diverticulitis	C	C	—
10	Intra-abdominal neoplasm	X	C	—
11	Intra-abdominal neoplasm	X	C	—
12	Intra-abdominal neoplasm	X	C†	Operative
13	Functional large bowel disease	C	C	—
14	Functional large bowel disease	X	C	—
15	Functional large bowel disease	C	C	—

C = Correct diagnosi
X = Incorrect diagnosi
* = Diagnosed at autopsy
† = Free rupture

Case 2.—A 70-year-old man entered the hospital with a seven-month history of vague, intermittent, para-umbilical pain, loss of 25 pounds in weight and constipation of recent origin. Physical examination by his private physician had shown a midabdominal mass. An upper gastrointestinal series and barium enema examination demonstrated an extrinsic mass displacing the stomach and transverse colon. Lateral displacement of the ureters was seen on an intravenous pyelogram. The patient was transferred to the hospital with a diagnosis of retroperitoneal sarcoma. At the time of admission it was noted that the mass was pulsatile and a diagnosis of abdominal aortic aneurysm was made. The aneurysm was resected. The postoperative course was uneventful and the patient was discharged asymptomatic. By the time of his first follow-up visit he had regained his previous weight and his bowel habits had returned to normal.

Case 3.—A 72-year-old man was awakened from sleep the morning of admission with acute onset of pain in the left lower quadrant of the abdomen. He described the pain as sharp, noncolicky and radiating into the left flank. An abdominal aortic aneurysm was found on physical examination. Tenderness in the left lower quadrant was believed to be unassociated with the aneurysmal mass. A diagnosis of diverticulitis was made and the patient was admitted to hospital. Barium enema examination showed a few diverticula, but no evidence of inflammation (Figure 1). Following this study, it was assumed that the patient's symptoms were secondary to the aneurysm. Aneurysmectomy was performed. The postoperative course was unremarkable and the patient was asymptomatic at the time of discharge.

Case 4.—A 69-year-old man entered the hospital with cramping lower abdominal pain of three days' duration. The patient said that he had passed no stool in that time but had passed some flatus. He also gave a history of intermittent episodes of melena for the preceding month. Upon physical examination the temperature was 37.9°C (100.2°F). Right lower quadrant abdominal tenderness was present. The admitting diagnosis was large bowel obstruction. Three hours after admission, while work-up was in progress, the severity of pain suddenly increased and radiated to the back. Following this, the patient collapsed and became pulseless. Blood pressure was unobtain-

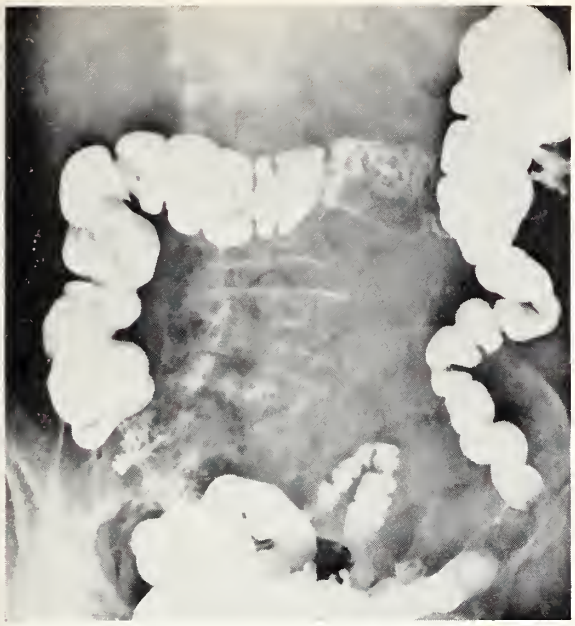


Figure 1.—Barium enema study showing sigmoid diverticula without inflammation. In addition, this film demonstrates a calcified abdominal aortic aneurysm, the visualization of which led to making the correct diagnosis.

able. Abdominal exploration was carried out immediately and a large ruptured aneurysm was found. Control of the aneurysm was obtained but the patient died on the operating table.

Discussion

Symptoms produced by abdominal aortic aneurysms have erroneously implicated every organ below the diaphragm.[4] The intestinal tract and the genitourinary system are the organs most commonly misdiagnosed as the source of distress produced by aortic aneurysms.[2-5,9,11]

In the present series, simulation of large bowel disease was the most common misleading symptom. The patients' complaints included lower abdominal cramping pain, anorexia and loss of weight. Some patients noted a change in bowel habits or abdominal distention. The diagnosis most commonly made was carcinoma and the second was diverticulitis. The clinical manifestations were at times so serious that bowel obstruction was diagnosed. Why an abdominal aortic aneurysm may cause symptoms in the large bowel is not clear. It may represent nerve root compression, or simply compression by the expanding aneurysm of an area of large intestine[10] (Figure 2). During physical examination, confusion as to the source of tenderness between an aneurysm and the sigmoid colon is understandable because of their close

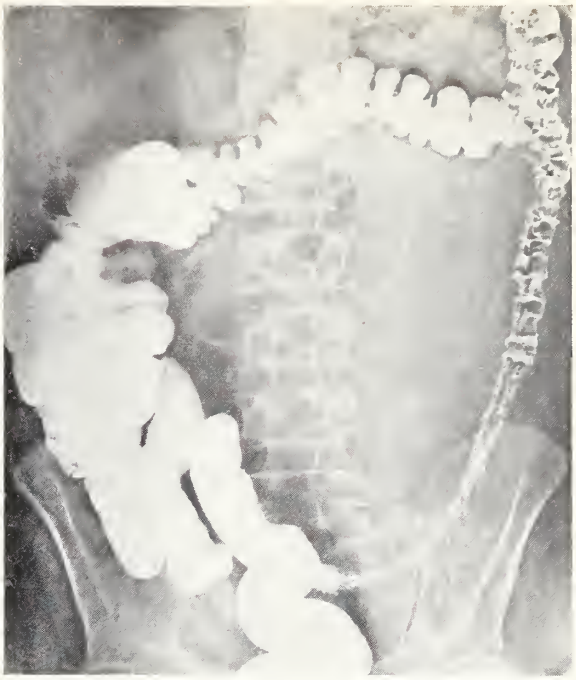


Figure 2.—Barium enema study in a patient with symptoms referable to the colon demonstrated displacement of the descending and sigmoid colon by a large retroperitoneal hematoma from a ruptured aneurysm.



Figure 3.—Lateral film of the abdomen demonstrating a calcified abdominal aortic aneurysm.

topographical relationship; in fact, in one patient aneurysmal pulsations were detected during sigmoidoscopy. The patient's complaints may so mimic those associated with colonic carcinoma that even when an aneurysm is known to be present, it may not be considered responsible for the

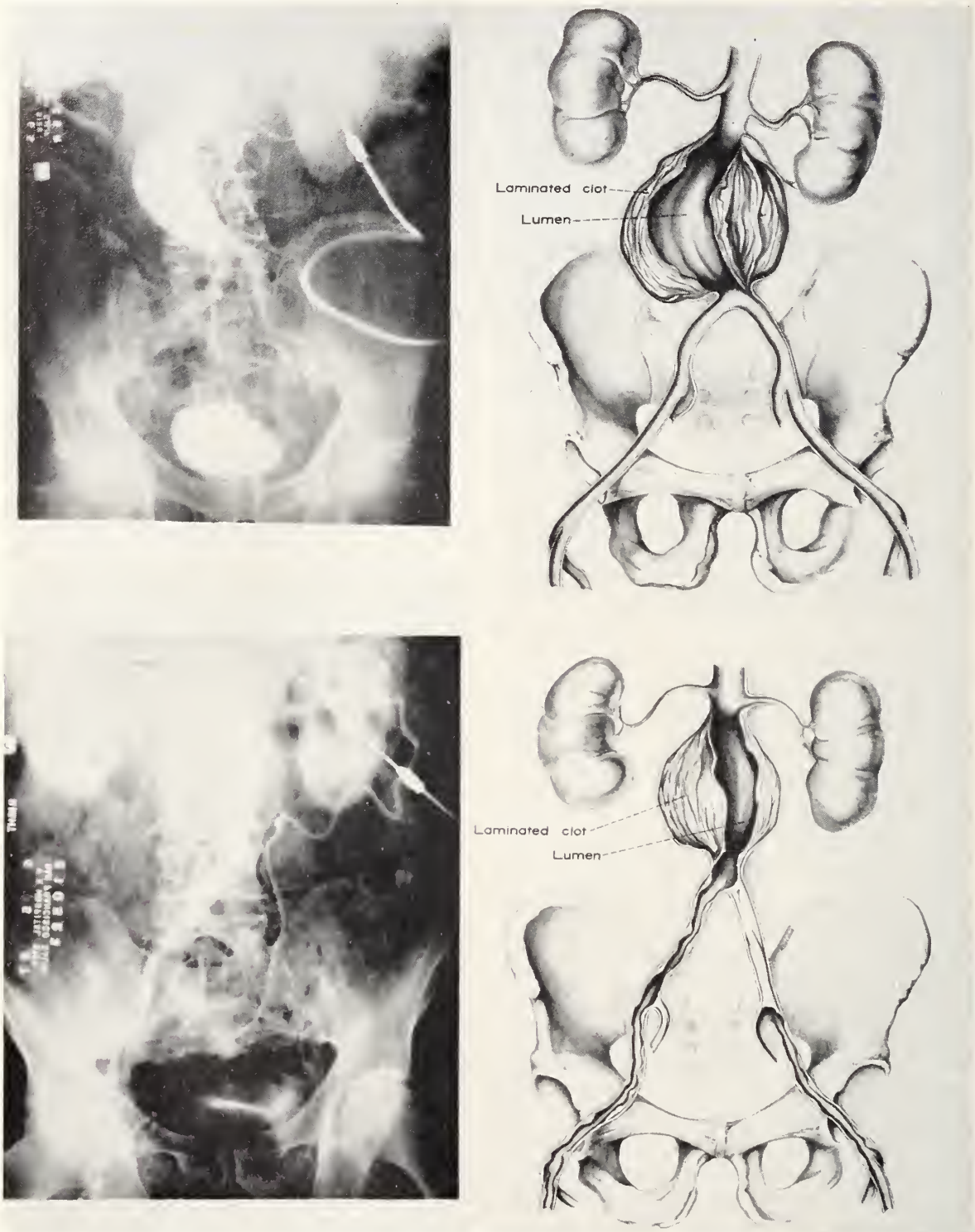


Figure 4.—The discrepancy between the actual size of the aneurysm as shown in the illustrations and the apparent size as seen in the aortograms is demonstrated. The difference in size is accounted for by the thickness of laminated clot within the aneurysm.

symptoms. The diagnosis of aneurysm may be further obscured by the presence of abdominal guarding and ileus.[7]

The next most common misdiagnosis in patients with abdominal aneurysm is disease of the genitourinary tract. This association was first described by Uhle in his report of five cases of aneurysm which were erroneously diagnosed as renal stone or perinephric abscess or ureteral colic.[11] The pain simulates that of renal colic, it originates in one or both flanks and may radiate to the groin and testicle.[3] Rob and Williams said that groin pain caused by an expanding aneurysm does not radiate into the testes and so may be differentiated from renal colic.[7] This has not been our experience. The pain is usually of sudden onset and may be associated with microscopic hematorrhea.[3] The cause of this pain pattern in symptomatic abdominal aneurysm is unknown, but it has been suggested that it may result from displacement of kidney and ureter, hemorrhage into the perinephric space, erosion of the vertebral bodies or nerve root compression.[10]

In other published series it has been suggested that a symptomatic aneurysm is often misdiagnosed as a peptic ulcer because epigastric distress is a frequent symptom of abdominal aneurysm.[3,7] The close association between the third portion of the duodenum and the aneurysm may explain those symptoms. A review of the literature by Sondheimer and coworkers included eight cases in which an enlarging aneurysm actually caused duodenal obstruction.[9] We have not seen such cases. Other erroneous diagnoses that have been reported include inguinal hernia, fibroid uterus, hypertension, abdominal tumor, appendicitis, spondylitis, cholecystitis and prostatitis.[8,10]

A correct diagnosis of symptomatic abdominal aneurysm can be made if one is aware of the unusual symptoms that it may produce and a careful physical examination is performed. If an aneurysm is not palpated, or if it is palpated but its significance is not recognized, an early diagnosis of symptomatic abdominal aortic aneurysm cannot be made. In most abdominal aortic aneurysms, calcification is present in the aneurysmal wall; thus, if anteroposterior and left posterior oblique films of the abdomen are obtained, the aneurysm will usually be outlined by a rim of calcification. A measurement of 5 cm or greater between the anterior and posterior walls of calcification is diagnostic for aneurysm (Figure 3).

In the few aneurysms without calcification, translumbar aortography has been helpful in making a diagnosis. The total diameter of an aneurysm is usually not visualized by aortography because of the presence of intraluminal laminated clot. However, the radiographic appearance of most aneurysms is characteristic enough to enable one to make an accurate diagnosis. This is especially true if oblique views are obtained during aortography (Figure 4).

The mortality rate associated with untreated abdominal aneurysms is high and is comparable to that of carcinoma of the breast.[5] Barratt-Boyes reported that the mortality rate was 47 percent after one year and 73 percent after three years in a group of patients with aneurysms who were not operated upon.[2] If an aneurysm is symptomatic at the time of examination, the mortality rate in patients who are not operated upon is even higher. Aneurysmectomy with grafting is now a well established mode of therapy. In the present series the mortality rate following elective aneurysm resection was 3 percent. Prompt diagnosis of abdominal aortic aneurysm as the source of abdominal distress will lead to early operative therapy and lowered mortality.

REFERENCES

1. Allen, E. V., Barker, N. W., and Hines, E. A. Jr.: Peripheral Vascular Diseases, ed 3, W. B. Saunders Co., Philadelphia, 1962, p. 438.

2. Barratt-Boyes, B. G.: Symptomatology and prognosis of abdominal aortic aneurysm, Lancet, 2:716, Oct. 1957.

3. Culp, O. S., and Bernatz, P. E.: Urologic aspects of lesions in the abdominal aorta, J. Urol., 86:189, Aug. 1961.

4. Enselberg, C. D.: The clinical picture of aneurysm of the abdominal aorta, Ann. Int. Med., 44:1163, June 1956.

5. Estes, J. E.: Abdominal aortic aneurysm: A study of one hundred and two cases, Circulation, II:258, Aug. 1950.

6. Harrison, T. R., Adams, R. D., Bennett, I. L., Resnik, W. H., Thorn, G. W., and Wintrobe, M. M.: Principles of Internal Medicine, ed 5, Blakiston Division, McGraw-Hill Book Co., New York, 1966, p. 717.

7. Rob, C. G., and Williams, J. P.: The diagnosis of aneurysms of the abdominal aorta (An analysis of 100 patients), J. Cardiov. Surg., 2:55, Jan. 1961.

8. Schanno, J. F., Ferre, J., and Asif, S.: Abdominal aortic aneurysms, Med. Ann. D. C., 34:413, Sept. 1965.

9. Sondheimer, F. K., and Steinberg, I.: Gastrointestinal manifestations of abdominal aortic aneurysms, Am. J. Roentgenol., 92:1110, Nov. 1964.

10. Szilagyi, D. E., Smith, R. F., Macksood, A. J., and Whitcomb, J. G.: Expanding and ruptured abdominal aortic aneurysms, Arch. Surg., 83:395, Sept. 1961.

11. Uhle, C. A. W.: The significance of aneurysm of the abdominal aorta masquerading as primary urologic disease, J. Urol., 45:13, Jan. 1941.

Phenylketonuria

Experience at One Center in the First Year of Screening in California

RAYMOND M. PETERSON, M.D., *Newport Beach*, RICHARD KOCH, M.D., GRACIELA E. SCHAEFFLER, P.H.N., AUDREY WOHLERS, P.H.N., PHYLLIS B. ACOSTA, M.S., AND DAVID BOYLE, M.D., *Los Angeles*

■ *One year's experience with phenylketonuria during the calendar year 1966, the first year for compulsory newborn screening in California, was reviewed. The over-all prevalence rate from reported cases in California during this period was one case per 19,500 persons tested. Fifty-seven persons suspected of having* PKU *were evaluated, and 25 of them were determined to be phenylketonuric. Eleven of the 25 were infants in whom the abnormality was detected through the newborn screening program or because it was detected in a sibling through a screening program. All the newborn phenylketonuric patients were developing normally at the time of last report (although the follow-up periods were short).*

In nine of the other children, PKU *was detected because they were retarded. Five retarded children who were diagnosed as phenylketonuric at another clinic were given dietary assistance.*

Five additional infants had elevated serum phenylalanines but did not have the classic biochemical findings of PKU *and are being evaluated further. Nine infants with positive screening tests exhibited biochemical and clinical findings consistent with transient tyrosinemia. Eighteen other children were evaluated and found to have no metabolic abnormality.*

The newborn screening program for PKU *is of decided benefit in early identification of a group of infants who have a high rate of potentially serious metabolic disease. Early identification permits treatment soon enough to prevent mental retardation. Newly identified patients should be evaluated in a medical setting capable of careful pediatric, biochemical and nutritional surveillance.*

On 29 October 1965 the California State Board of Health adopted regulations (Sec. 6500, Title 17) on testing for phenylketonuria (PKU) to conform with Assembly Bill 12 passed by the California Legislature in 1965. This regulation, which became effective 1 January 1966, requires physicians to order an approved test for PKU on all newborn infants and on infants of age 30 days or under when admitted to another hospital. The physician must also arrange for a repeat test within seven days of notification if the initial test is presumptively positive. The provisions of this section do not apply if the parent or legally appointed guardian objects to the test on the grounds that it conflicts with his religious beliefs or practices, or if it is determined by the patient's physician that there are medical contraindications to the procedure.

Tests approved for use by the State Health Department are the Bacterial Inhibition Assay[7] and the Fluorimetric Procedure,[14] which have both been found to be effective.[11] There are 202 approved public and private laboratories in California doing these studies (60 Fluorimetric, 113 Inhibition Assay and 29 both). California is unusual in that most other states require that the tests be performed in a centralized state laboratory.

In some areas of the country, routine blood testing has been performed since Guthrie[6] described a simplified method in 1961. Irwin[8] reported that a successful routine nursery screening program has been in operation at Sharp Memorial Community Hospital in San Diego since August of 1963. Mandatory testing laws in the United States first appeared in 1963 when Massachusetts passed such a law, and there are now 37 states with laws requiring testing.[17]

After one calendar year of testing newborns in California, it was thought fitting to review the results in light of the experience gained at the PKU Clinic, Childrens Hospital of Los Angeles. This is timely in the light of recent criticism regarding the value of routine testing.[2]

According to figures from the California State Board of Health,[4] 311,953 infants were tested in 1966 and 16 cases of PKU were discovered, for a prevalence rate of one case per 19,497 tested. Five additional infants with hyperphenylalaninemia were identified. If these are included, the prevalence rate would be one per 14,855. The reason for the variation in incidence in different series, such as reported in Massachusetts,[13] is unclear.

The PKU Clinic at Childrens Hospital of Los Angeles serves as one of the centers authorized by the Bureau of Crippled Children of the State Health Department for diagnosis and treatment for Southern California (See Appendix). Most children resided in Los Angeles County, but one-third were received from other Southern California counties, two from military installations located in Southern California, one from a bordering state and two from foreign countries (See Table 1). On four occasions individual parents without a family physician requested help and were assisted.

When a request for assistance with the care of a patient suspected of having phenylketonuria was received, all team members were alerted. If the serum level was significantly elevated, above 12 to 15 mg per 100 ml (normal 2 to 4 mg), arrangements were made for admission to the hospital for complete diagnostic evaluation. However, if the serum phenylalanine level was only slightly elevated (6 to 12 mg per 100 ml), or if satisfactory laboratory studies had not been performed, a public health nurse was requested to obtain serum for phenylalanine and tyrosine determinations, and urine for amino-acid chromatography. The need for admission to hospital and follow-up evaluations was based upon the results of these initial studies. The diagnosis of PKU was considered confirmed when the serum phenylalanine was persistently greater than 20 mg per 100 ml, the serum tyrosine

TABLE 1.—*Source of Referrals for PKU Testing at Childrens Hospital, Los Angeles, by County*

Geographic, by county:	
Los Angeles	33
Santa Barbara	4
San Bernardino	4
Riverside	3
Orange	2
Ventura	2
San Diego	2
Kern	1
San Luis Obispo	1
Other	
Military	2
Vandenberg Air Force Base Morro Bay	
Arizona	1
India	1
Venezuela	1
TOTAL	57

From the PKU Collaborative study, Department of Pediatrics, University of Southern California School of Medicine and the Division of Child Development, Childrens Hospital of Los Angeles. Supported by grants from the Children's Bureau and the Division of Mental Retardation, Public Health Service, Department of Health, Education, and Welfare, Washington, D.C., and the See's Candy Foundation.

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Reprint requests to: Director, Child Development Division, Childrens Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles 90027 (Dr. Koch).

remained within normal limits and urine amino-acid chromatography revealed the classic metabolites consistent with PKU. After confirmation of diagnosis, the low-phenylalanine diet was instituted. In confirmed cases, serum phenylalanine levels were obtained on parents and siblings. In special cases, loading procedures were also performed on family members. Hospital discharge occurred when the serum phenylalanine approached normal, and the family was counseled regarding the disease and dietary treatment.

In case of any question regarding specific diagnosis, periodic tolerance tests were performed by increasing dietary protein. To ascertain that serum levels returned to normal but not to subnormal values, regular serum phenylalanine levels were obtained at weekly intervals, or in a few cases as often as every other day, by either the fluorimetric or inhibition methods. If the serum tyrosine was significantly elevated and transient tyrosinemia suspected, Vitamin C was prescribed, and the patient followed closely as an outpatient.

During the year 1966 there were 20 new confirmed cases of PKU identified by the clinic (Table 2). Eight infants were identified by routine newborn screening. Screening siblings of the eight newborn cases resulted in the identification of two older children. Another infant was identified during the first week of life because PKU had already been diagnosed in an older sibling. The condition in this child most likely would have been picked up by routine screening even had the known family history of PKU not resulted in special studies of this high risk patient.

In nine other children, ages six months to six and one-half years, PKU was initially diagnosed because the child was mentally retarded. Five other retarded children in whom PKU had previously been diagnosed elsewhere, were seen by the clinic staff for the first time in 1966 for assistance in management. Five children were tentatively identified as hyperphenylalaninemic. (These infants may later be identified as having PKU, or some other type of metabolic abnormality may be demonstrated.) There were five proven and four suspected cases of transient tyrosinemia. All of these presented with slightly elevated serum phenylalanine (6 to 12 mg per 100 ml) and elevated serum tyrosine levels (greater than 3 mg per 100 ml). Serum phenylalanine and tyrosine levels returned to normal within a few days or weeks after Vitamin C supplements were added to their diets. Five retarded children were evaluated because they were suspected of having PKU but subsequent tests did not confirm this. Thirteen other infants with slightly elevated serum phenylalanine levels initially, were found to be normal.

TABLE 2.—*Sources of Referral, by Physician or Other*

Pediatricians	20
General Practitioners	18
Public Health Department	8
PKU Clinic (Screening)	6
Self Referrals	4
Obstetrician-Gynecologist	1
TOTAL	57

Discussion

It is beyond the scope of this paper to discuss all aspects of the detection and diagnosis of phenylketonuria. However, such material is the subject of a recent review by Cunningham.[5] We are presenting the experience gained during the evaluation of 57 children referred to the PKU Clinic during the first calendar year in which compulsory testing of newborns was in effect in California.

While the exact cause of mental deterioration is not yet fully understood, studies from both institutional and non-institutional sources have shown that untreated PKU children frequently exhibit mental retardation. In our experience, and that of others, if the maximum benefit is to be derived from the low-phenylalanine diet, diagnosis must be made and therapy begun early in life.[3,9,10,12]

Widespread screening has shown that not all newborns with hyperphenylalaninemia are necessarily phenylketonuric. For this reason it is necessary to make certain that the diagnosis is well established before treatment is begun. We have

TABLE 3.—*Data on Diagnosis in 57 Patients Referred for PKU Testing*

PKU (New)		20
Newborn Screening	8	
Sibling Screening After Newborn Detected	2	
Newborn Sibling of Known PKU	1	
Screened Because of Mental Retardation	9	
PKU (Known)		5
Referral for Assistance in Care		
Hyperphenylalaninemia		5
Transient Tyrosinemia		9
Proven	5	
Suspected	4	
Retarded Children (Not PKU)		5
Newborn suspected (Normal)		13
TOTAL		57

arbitrarily divided the patients evaluated during 1966 into six groups: (1) PKU (New), (2) PKU (Known), (3) hyperphenylalaninemia of undetermined cause, (4) transient tyrosinemia, (5) mentally retarded: not PKU, and (6) a group of normal newborns in whom no evident metabolic abnormality was detected. Other specific metabolic abnormalities have been reported to cause false positive reaction to PKU screening tests, but we did not encounter any such cases. The children whom we have classified as hyperphenylalaninemic may eventually be determined to have PKU or metabolic disorder of some other type.

Children with biochemical evidence of phenylketonuria, (significantly protracted elevated serum phenylalanine, a normal serum tyrosine and urine showing significant amounts of phenylalanine, phenylpyruvic acid and its metabolites to include orthohydroxyphenylacetic acid) should receive a low-phenylalanine diet as soon as the diagnosis is confirmed. Those with only slightly elevated serum phenylalanine levels, normal serum tyrosine and normal or slightly elevated urinary phenylalanine and its metabolites (hyperphenylalaninemia) should be on a modified diet containing limited amounts of protein, with periodic protein challenges and close observation. Transient tyrosinemia is considered to produce no consistent clinical syndrome,[1] and in general can be considered benign. Infants with this finding should be allowed to continue on a normal diet with supplementary ascorbic acid (Vitamin C) in the range of 100 mg per day until serum phenylalanine and tyrosine levels reach normal. Obviously those with no demonstrated metabolic defect should be allowed to continue a normal diet.

Diets deficient in protein or in specific essential amino acids should not be given unless a metabolic defect is present in which excess of either the substance itself or of its metabolites is detrimental to the functioning or development of the patient. Decreased growth,[16] severe anemia,[15] and skin rash have been described in patients who did not receive adequate dietary phenylalanine. Since phenylalanine is an essential amino acid to life, even death could occur with severe prolonged deprivation. It is imperative, therefore, that the diagnosis of PKU be confirmed, and that when the diet is instituted it be properly monitored. The commercially available low-phenylalanine formula, Lofenalac,* is effective in reducing serum levels of phenylalanine in phenylketonuric patients, but it should never be prescribed without supplemental phenylalanine, for even a phenylketonuric person requires exogenous phenylalanine.

Several patients in our series were started on Lofenalac before adequate diagnosis was made, and two of these, who later were determined to have PKU, had dangerously subnormal serum phenylalanine levels when initially evaluated. One patient was started on Lofenalac without additional protein when the physician misinterpreted the results of a normal screening test.

Because of the need for accurate diagnosis, the prescription of proper diet, monitoring of serum phenylalanine and counseling over a long term, it is recommended that these functions be performed by a multi-disciplinary team which includes a pediatrician, a nutritionist, a biochemist, a public health nurse and a psychologist. The routine medical care should be provided by the family physician. Accordingly, patients that we dealt with were cared for in conjunction with their family physician. However, the clinic personnel continued to follow all infants with confirmed PKU to study their nutritional needs and development.

*Produced by Mead, Johnson Incorporated, Evansville, Indiana.

REFERENCES

1. Avery, M. E., Clow, C. L., Menkes, J. H., Ramos, A., Schriver, C. R., Stern, L., and Wasserman, B. P.: Transient tyrosinemia of the newborn: Dietary and clinical aspects, Pediatrics, 39:378-384, Mar. 1967.

2. Bessman, S. P.: Legislation and advances in medical knowledge—Acceleration or inhibition? J. Pediat., 69: 334, Aug. 1966.

3. Bickel, H., and Gruter, W. P.: Prophylaxe und Behandlung der Phenylketonurie (Prophylaxis and Treatment of Phenylketonuria), Deutch Med. Wschr., 86:39-43, Jan. 1961.

4. California State Department of Public Health, Personal Communication, Mar. 1967.

5. Cunningham, G. C.: Phenylketonuria: Early detection, diagnosis and treatment, Calif. Med., 105:1, July 1966.

6. Guthrie, R.: Blood screening for phenylketonuria, JAMA, 178:863, Nov. 25, 1961.

7. Guthrie, R., and Susi, A.: A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants, Pediatrics, 32:338-343, Sept. 1963.

8. Irwin, H. R., Notrica, S., and Fleming, W.: Blood phenylalanine levels of newborn infants — A routine screening program for the hospital, Calif. Med., 101:331, Nov. 1964.

9. Kang, E. S., Kennedy, J. L., Jr., Gates, L., Burwash, I., and McKinnon, A.: Clinical observations in phenylketonuria, Pediatrics, 35:282, Aug. 1963.

10. Koch, R., Acosta, P., Fishler, K., Schaeffler, G., and Wohlers, A.: Clinical observations on phenylketonuria, Am. J. Dis. Child., 113:6, Jan. 1967.

11. Koch, R., Williamson, M. L., Donnell, G. N., Guthrie, R., Straus, R., Coffelt, R. W., and Fish, C. H.: A cooperative study of two methods for phenylalanine

determination: McCaman-Robins Fluorimetric and microbiological inhibition methods, J. Pediat., 68:905, June 1966.

12. Knox, W. E.: An evaluation of the treatment of phenylketonuria with diets low in phenylalanine, Pediatrics, 26:1, July 1960.

13. Massachusetts Department of Public Health: Screening program for phenylketonuria and other inborn errors of metabolism, New Eng. J. Med., 273:109, 8 July 1965.

14. McCaman, M. W., and Robins, E.: Fluorimetric method for the determination of phenylalanine in serum, J. of Lab. Clin. Med., 59:885, May 1962.

15. Royston, N. J. W., and Parry, T. E.: Megaloblastic anemia complicating dietary treatment of phenylketonuria in infancy, Arch. Dis. Child., 37:430, Aug. 1962.

16. Rouse, B. M.: Phenylalanine deficiency syndrome, J. Pediat., 69:246, Aug. 1966.

17. U.S. Department of Health, Education and Welfare, Welfare Administration, Children's Bureau—State laws pertaining to phenylketonuria as of Nov. 1966, 1967.

Appendix I

Medical centers approved by the Bureau to provide consultation and evaluation in phenylketonuria:

1. Peter Cohen, M.D., Neurological Diagnostic Center, U.C.-Moffitt Hospital, Third and Parnassus Streets, San Francisco, California 94122.

2. Richard Koch, M.D., Division of Child Development, Childrens Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles, California 90027.

3. Thomas Nelson, M.D., White Memorial Hospital, 1720 Brooklyn Avenue, Los Angeles, California 90033.

4. Edward Senz, M.D., Neurological Diagnostic Center, Children's Hospital Medical Center of Northern California, 51st and Dover Streets, Oakland, California 94609.

5. Richard Umansky, M.D., Child Development Center, Children's Hospital Medical Center of Northern California, 51st and Dover Streets, Oakland, California 94609.

6. Stanley Wright, M.D., University of California Medical Center, 405 Hilgard Avenue, Los Angeles, California 90024.

7. Bernard Rudis, M.D., Neurological Diagnostic Center, Valley Children's Hospital, 3151 North Millbrook Avenue, Fresno, California 93703.

8. Robert E. Greenberg, M.D., Stanford Medical Center, Palo Alto, California 94304.

9. Robert F. Chinnock, M.D., Loma Linda University Hospital, Loma Linda, California 92354.

CORRECTION

An error was made in a sentence in the article "Fractures of the Calcaneus" by Carl E. Horn, M.D., which appeared in the March issue of California Medicine. The sentence which begins "Protruding bone," in the paragraph starting a little below mid-way of the right-hand column on page 213 is corrected as follows: "Protruding bone from the lateral border of the calcaneus was excised and subtalar arthrodesis performed. Films taken five months following operation showed clearly the residual shortening in length and height of the tuberosity with resultant poor structure of the hind-foot."

Anesthetic Complications and Deaths

JOHN W. PENDER, M.D., *Palo Alto*

■ *Anesthesiologists should fully inform patients of the possible complications from anesthesia. For rapport with the patient, with whom they usually have no acquaintance until a day or so before an operative procedure, the anesthesiologist should enlist the help of the internist or surgeon who already has established an atmosphere of trust.*

The extent of morbidity and minor complications from anesthesia has not been adequately recorded.

One out of every 1,000 to 2,000 anesthetized patients dies of complications primarily due to or contributed to by anesthesia.

Leading causes of death vary from study to study and from year to year.

FACTUAL INFORMATION about the true incidence and severity of complications associated with anesthesia is not adequately communicated to the average surgical patient. Too often the patient's inquiries about forthcoming anesthesia are lightly dismissed with the explanation that there will be nothing to it but a "shot in the arm." Primary responsibility for education of the patient lies with the anesthesiologist but he is hampered by his brief acquaintance with the patient, which occurs soon after admission to the hospital and at a time when the patient is distracted by many other apprehensions. Aid of the internist and surgeon, in whom the patient already has confidence, is needed for correctly informing him about complications which may occur during and after anesthesia. Only in this manner can resentment be avoided. The patient who has an anesthetic complication after having been led to believe that none ever occurs, naturally assumes that someone has been negligent.

The purpose of this paper is to review and compare some of the studies which have been made about the character and incidence of complications associated with anesthesia in various parts of the world. Sections will be devoted to legal aspects, non-fatal complications and fatal complications.

Submitted 23 June 1967.

Reprint requests to: Palo Alto Medical Clinic, 300 Homer Avenue, Palo Alto 94301.

Legal Aspects

Of the legal aspects, only the principles of *res ipsa loquitur* and *informed consent* will be discussed.

According to the principle of *res ipsa loquitur,* the court may rule that the plaintiff does not need to prove negligence on the part of the defendant but instead may call on the defendant to explain his actions. In 1944 a California court ruled that when a plaintiff receives unusual injuries while unconscious and in the course of medical treatment, all those defendants who had any control over his body or the instruments which might have caused the injuries could properly be called upon to meet the inference of negligence by giving an explanation of their conduct.[11] This indicates that anesthesiologists and surgeons share each others' complications.

Physicians are inclined to be paranoid about

application of this legal procedure and believe that their rights are being infringed when they are considered guilty until they prove themselves innocent. However, a similar philosophy is being applied in other areas of human relations. At one time an injured employee had to prove negligence on the part of his employer before damages would be awarded. Now the disabled employee is considered a responsibility of society and is supported by increasingly generous workmen's compensation laws.

Modern juries rarely spend much time trying to decide responsibility for cause of automobile accidents. Emphasis is put on the amount of damages to be paid and which insurance company shall pay them. Ultimately insurance companies are social institutions representing large portions of the population. Similarly, when a patient is disabled by an anesthetic complication, the insurance company of either the physician or the hospital is the most likely source of compensation to the patient for his disability.

Consent for a medical procedure to be performed is based on the patient's information about its advantages and disadvantages. In 1960 the Supreme Court of Missouri declared that a physician owes his patient a duty to inform him, generally, of the possible serious collateral hazards.[12] It is impossible to acquaint the patient adequately with every possible complication associated with anesthesia, but there is no justification for misinforming the patient by either direct or implied statements.

Non-Fatal Complications

The total incidence of non-fatal anesthetic complications in large groups of patients has not been reported adequately. Most studies have been of one isolated complication or a related group of complications. Departmental annual reports rarely give any detail about temporary non-fatal anesthetic complications.

An exceptional study was that reported by Edmonds-Seal and Eve[5] in which an attempt was made to elicit as many complaints as possible from patients on the first and second day after general anesthesia. In spite of early inexperience of the single interrogator, 47 percent of 513 patients admitted to at least one of the complications listed in Table 1. In general the incidence of complications noted by these observers agrees reasonably well with that reported in other studies in which only single complications were investigated. The incidence of generalized muscle pains in patients who had received a depolarizing muscle relaxant was less than that reported by some investigators, but this was explained by the fact that the patients of Edmonds-Seal and Eve had not been ambulatory at the time of questioning.

TABLE 1.—*Non-Fatal Complications Following General Anesthesia in 513 Cases**
(Overall Incidence, 47 Percent)

	Patients	*Percent of Total*
Vomiting	113	22.0
Bruises	73	14.2
Sore throat	72	14.0
Backache	25	4.9
Pain in jaw	16	3.1
Headache	14	2.7
Cough	11	2.1
Pain in heel	11	2.1
Pain in knee	9	1.7
Pain in elbow	9	1.7
Dental trauma	6	1.2
Bruise lip	5	0.9
Muscle pain	4	0.7
Pain in eye	3	0.6
Pain over nose	2	0.4
Lacerated tongue	1	0.2
Temporary deafness	1	0.2
Temporary hand numbness	1	0.2
Skin necrosis after venipuncture	1	0.2

* Adapted from Edmonds-Seal and Eve.[5]

During routine post-anesthesia rounds, most anesthesiologists are too involved in trying to separate anesthetic from surgical complications to search for additional minor complaints.

Fatal Complications

During recent years many good studies have been made of the incidence and cause of fatal anesthetic complications. Before the report by Beecher and Todd[1] in 1954 on data from ten university hospitals, open discussion about fatal anesthetic complications was for the most part eschewed. The anesthetic mortality rate of 1 in 1,500 that was reported by Beecher and Todd is about the same as has been presented in subsequent reports.

In 1956 a committee appointed by the Council of Association of Anesthetists of Great Britain and Ireland studied 1,000 voluntary reports of deaths associated with anesthesia.[6] In the committee's opinion, 589 of the 1,000 deaths were in some degree attributable to anesthesia. A condensed summary of the etiological factors associated with fatal complications is given in Table 2. The complication with the highest incidence was regurgitation and vomiting, with overdose of intravenous barbiturate a close second. Anesthesiologists

TABLE 2.—*Anesthetic Deaths in England**
Causes of 589 Deaths Attributed to Anesthesia

	Deaths	Percent of Total
Regurgitation—Vomiting	110	18.6
Overdose I. V. barbiturate	107	18.1
Inadequate resuscitation	49	8.3
Endotracheal intubation	41	6.9
Post-op respiratory obstruction	33	5.6
Inadequate ventilation	26	4.4
Spinal and epidural	25	4.2
Induced hypotension	17	2.9
Bronchospasm	16	2.7
Convulsion	15	2.6
Sudden death in children	14	2.4
Trichlorethylene	12	2.2
Apparatus	10	1.7
Chloroform	6	1.0

*Adapted from Edwards.[6]

TABLE 3.—*Anesthetic Deaths in Australia**
Causes of 55 Deaths—Estimated 1 per 2,000 Anesthetics

	Patients	Percent of Total
Overdose	27	49.0
Inadequate management of crisis	24	43.6
Inadequate preanesthetic preparation	22	40.0
Wrong choice of anesthetic	22	40.0
Inadequate ventilation	18	32.7
Inadequate resuscitation	11	20.0
Inadequate patient observation	6	10.9
Hypoxic gas mixture	5	9.0
Technical mishaps	5	9.0
Inadequate relaxant reversal	2	3.6
Inhalation of vomitus	1	1.8

*Adapted from Holland.[7]

TABLE 4.—*American Anesthetic Deaths*
Causes of 18 Primary Anesthetic Deaths (from Schapira[10])
Incidence: 1 to 1,232

Inadequate ventilation	8
Topical cocaine	4
Ventricular fibrillation	2
Wrong choice of drug	1
Overdose of cyclopropane	1
Laryngospasm	1
High spinal	1

learned early the dangers of administering general anesthesia to patients with full stomachs, but only in the past five or six years have surgeons stopped insisting that minor operations of short duration could be done safely with only a "shot of Pentothal."

After the committee's study was completed, reports continued to be received and 600 were reviewed by Dinnick[3] in 1964. Anesthesia was considered to have been implicated in about two-thirds of the deaths. Low blood volume due to hemorrhage, shock and dehydration was by far the leading cause of death and indicated that during the time interval between the two studies the anesthesiologist had assumed responsibility for maintenance of adequate circulation as well as respiration and anesthesia. Regurgitation and vomiting had fallen to third place as a cause of death and was considered to have been a cause of death less frequently than underventilation of the lungs.

In Australia, voluntary reporting of deaths associated with anesthesia was considered unsatisfactory and, since such cases are routinely reported to a coroner, an extensive questionnaire was sent to the anesthesiologist in charge of each patient at the time of death. Participation in this study was encouraged by declaring the information in the questionnaire confidential and thereby insuring anonymity. The information was reviewed by a committee representing several medical disciplines. Of 100 deaths, 55 were considered to have been partly or entirely caused by anesthesia, which made an estimated incidence of one death for about every 2,000 anesthetics administered in the area during the time of the study (Table 3). Overdose, inadequate management of crisis, inadequate pre-anesthetic preparation of the patient, and wrong choice of anesthetic were the leading causes of death and each was in about the same frequency as the others. Only one fatality was attributed to inhalation of vomitus. Credit for this low incidence was attributed to the publicity of the earlier mentioned English review, which may be taken as an indication of the efficacy of education and communication in the prevention of complications.

Since the 1954 report by Beecher and Todd[1] no broad-based American study on anesthetic mortality has been conducted with which to closely compare the English and Australian studies. However, localized American reports are more numerous. Schapira and coworkers[10] considered anesthesia to have been the primary cause of death in 18 of 22,177 patients who received anesthetic services, an incidence of one death for about 1,232 services (Table 4). Inadequate ventilation was the most frequent cause of death. Boba and Landmesser[2] divided the causes of cardio-respiratory collapse due to anesthesia into errors of commission and those of omission. The errors of omission were three times those of commission, which leads to the belief that the anesthesiologist knows how to maintain the safety of his patient but frequently reduces the margin of safety through yielding to pressure from other members of the operating team. The Baltimore Anesthesia Study Commis-

sion[9] reviewed 1,024 postoperative deaths and found anesthesia to be a primary or contributing cause of death in about one per 2,500 operations. Error in preoperative preparation and medication of the patient was considered the cause of 29 out of 196 anesthetic deaths, emphasizing the role of the anesthesiologist in sharing overall care of the patient with internist and surgeon.

Fires and explosions, once the most dreaded of anesthetic complications, have decreased in frequency. Although no reliable statistics are available, it has been estimated that during 1964 about 58 fires and explosions occurred during anesthesia in the United States, with a mortality rate to the patient of approximately 60 percent. Most of these accidents were attributed to static electricity due to loss of electrical conductivity in rubber that was considered to be conductive.

A report by Memery[8] on a large number of anesthetics administered in private practice indicates that the death rate approximates that found in institutional practice. The mortality rate primarily due to or contributed to by anesthesia for surgical operations, excluding obstetrics, was 1 death per 1,082 anesthetics. Inadequate monitoring of the patient and inadequate respiratory support were considered the two most frequently committed errors. As in the previous report by Dripps and others,[4] it was found that the incidence of death was greater following general anesthesia than after spinal anesthesia and the great majority of deaths occurred in patients with severe systemic disturbances.

REFERENCES

1. Beecher, H. K., and Todd, D. P.: A study of the deaths associated with anesthesia and surgery, Ann. Surg., 140:2, July 1954.

2. Boba, A., and Landmesser, C. M.: Total cardiopulmonary collapse. Contributing and causative errors of omission and commission for which the anesthesiologist must assume responsibility, N. Y. J. Med., 61:2928, 1 Sept. 1961.

3. Dinnick, O. P.: Deaths associated with anaesthesia, Anaesthesia, 19:536, Oct. 1964.

4. Dripps, R. D., Lamont, A., and Eckenhoff, J. E.: Role of anesthesia in surgical mortality, JAMA, 178:261, 21 Oct. 1961.

5. Edmonds-Seal, J., and Eve, N. H.: Minor sequelae of anaesthesia, Brit. J. Anaesth., 34:44, Jan. 1962.

6. Edwards, G., Morton, H. J. V., Pask, E. A., and Wylie, W. D.: Deaths associated with anaesthesia, Anaesthesia, 11:194, July 1956.

7. Holland, R.: Interim report of the special committee appointed to investigate deaths due to anaesthesia in New South Wales, Med. J. Aus., 49:575, 13 Oct. 1962.

8. Memery, H. N.: Anesthesia mortality in private practice, JAMA, 194:127, 13 Dec. 1965.

9. Phillips, O. C., Frazier, T. M., Graff, T. D., and Kornfield, T. J.: Baltimore anesthesia study committee—review of 1,024 postoperative deaths, JAMA, 174:2015, 7 Dec. 1960.

10. Schapira, M., Kepes, E. R., and Hurwitt, E. S.: An analysis of deaths in the operating room and within 24 hours of surgery, Anesth. Analg. (Cleveland), 39:149, Mar.-Apr. 1960.

11. Wasmuth, C. E.: Changing legal concepts, Anesth. Analg. (Cleveland), 41:521, July-Aug. 1962.

12. Wasmuth, C. E.: Changing legal concepts, Anesth. Analg. (Cleveland), 41:525, Sept.-Oct. 1962.



Tuberculosis Relapses

Failure to Use Chemoprophylaxis

W. H. OATWAY, JR., M.D., *Altadena*

TUBERCULOSIS IS NOT YET controlled, as everyone who knows current statistics and epidemiology is aware. There is a huge number of cases in the general population. Most of them are unrecognized, but in many instances the infected persons are known to have "scars," "spots," or "TB" that have been present for several months to many years.

Hardly any of the persons with recognized lesions have been examined for activity, and not many have had chemotherapy. Some of those who have had such treatment had it only for brief periods — weeks or months — and often quite a few years ago.

Chemotherapy for recently active tuberculosis has been given for lengthening periods in recent years, but constancy and extent still depend on the physician and the patient. The brevity of the periods of chemotherapy from 1947 to 1957 was due to the opinion about therapy in those years, to inadequate follow-ups, to intolerance or allergic sensitivity or to ignorance or carelessness on the patient's part.

The use of the anti-tuberculosis drugs to prevent either activity or relapse has been strongly recommended since 1959, when a "Letter to the Editor" of a major respiratory disease journal urged that failure to use the method was a major and serious gap in the use of chemoprophylaxis.

The present report deals with comparisons between two series of patients. One series was made up of 100 consecutive patients who were admitted to a small tuberculosis hospital in Southern California in 1962-63. The percentage of patients with previously known lesions, untreated by anti-tuberculosis agents, was determined. The other series comprised the same number of patients admitted to the same hospital in 1965-66. Both series included only patients who had lesions of tuberculosis (of one degree or another of activity) by current x-ray examination, and current evidence of tuberculosis by bacterial tests (concentrates and sputum or gastric aspirate cultures). X-ray studies before the patients were admitted to hospital were diligently sought from earlier sources and if the films were not available, verbal reports were requested. Data on previous bacterial tests and on the use of chemotherapy were obtained from the patients or their physicians.

An attempt was made to derive several simple conclusions from the data: (1) Was the case recognized as tuberculosis? (2) Was the patient adequately examined by bacterial tests? (3) Was a progressive lesion noted roentgenographically? (4) Was relapse preventable if there had been adequate diagnosis and treatment? (5) Where did responsibility for delay in diagnosis and therapy lie? (6) Was there any improvement in statistics between 1962-63 and 1965-66?

The survey brought to light not only serious gaps in therapeutic follow-up in cases of known pulmonary lesions, but dismaying inadequacy of records (and memory) needed for obtaining information from physicians, hospitals and patients as to history of diagnosis and previous treatment.

It was found that a high proportion of the patients studied had lung lesions that were known

From La Vina Sanatorium and Hospital, Altadena. This report was presented to the California Sanatorium Association and to the attending staff at the Los Angeles County General Hospital, April and May, 1967.

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about, from x-ray films, for from 8 months to 38 years before current active disease was diagnosed (Table 1). These patients had poor follow-up, inadequate bacterial tests and almost no chemotherapy or chemoprophylaxis against relapse. The findings among 100 patients in 1965-66 were the same as those three years earlier, in 1962-63.

There were many obstacles to obtaining data on previous examinations and treatment and to finding previous x-ray films for comparison. Frequently patients could not remember the dates or places of x-ray examination or bacterial tests, or even whether they had ever had either. Sometimes x-ray films were known to have been made but had been discarded or misplaced or for other reasons were not obtainable. It was found also that history-takers might fail to record the taking of x-rays. Information on dates and duration of chemotherapy was often equally obscure.

Responsibility for delays in medical care—diagnosis or therapy — lay sometimes with physicians, sometimes with health departments, sometimes with the patients. In some instances all were in some degree culpable.

Reasons referable to the patients were that they had not been told they had the disease, they did not know the significance of x-ray findings (scars, pneumonia, pleurisy) or they did not want to know (or would not believe) that they had tuberculosis. They might drift away from therapeutic care, with only a few being known as tuberculous. Obtaining information from them was occasionally difficult because of evasiveness or recalcitrance.

Weaknesses in the machinery for medical follow-up of patients were of several orders. Among general physicians, failure to keep patients under observation might be because the physicians accepted reports of x-ray readers ("no active tuberculosis"; "a few old scars, inactive" and the like); or they might neglect to report cases to the Health Department and then themselves lose contact with the patient. Chest specialists may not be able to continue the consultant care, and in some cases

TABLE 1.—*Results of the Surveys of Two Series of 100 Cases Each*

	Number of Cases	*Pre-Sanatorium x-ray showing TB present*	*Additional reports of lesions*	*Total*	*Patients with previous bacterial tests*	*Patients with previous chemotherapy*
1. First Series (1962-1963)	100	60	18	78 percent	about 10 percent	about 20 percent
2. Second Series (1965-1966)	100	65	12	77 percent	about 15 percent (1 or 2 sputum concentrates, rare cultures)	about 15 percent

*Examples of duration of lesions**

Age	*Duration of lesion (Years)*
68	17
40	4
60	4
17	12
45	27
30	14
44	5
45	4
42	16
65	1½
30	1½
70	2½
61	6
65	18
65	2-9
54	14
69	9, 4 and 2
68	38, 22 and 4
62	6
66	12

*Estimate of reason and fault for delay**

M.D.s	*Chest Specialists*	*X-ray Laboratories*	*Health Dept.*	*Patient*
				X
X				
X			X	X
			X	X
X			X	
			X	X
X		X		
X				X
			X	X
X		X		
			X	
X			X	
X				
X				X
				?
X(2)				
			X	XX
X				X
X(2)				
				X

*Every fifth case was chosen from the first series. Findings for the second series were similar.

they may be over-confident that "inactive" lesions will continue quiescent.

X-ray clinics often are limited to single x-ray films for diagnosis of activity and they may not have previous films at hand for comparison. A lesion may be called "inactive" without bacterial proof.

Health departments must depend for the most part on reports from physicians for case-finding, and in the past they had to depend on the constancy of patients. Now, with more adequate staffs, they do a very good job of tracing patients who change address, often keeping them under observation for years.

Discussion

From the foregoing it is obvious that action is needed on many fronts to correct present shortcomings.

The public still needs education about tuberculosis. Certainly the patient does, since delay in care and interruption of therapy are often traceable to ignorance or neglect on his part.

What the health care community is doing, at all levels of medicine and public health, is better than in past years, but it is not good enough. We must work harder at case-finding by x-ray surveys, perhaps with help of skin tests, and we must diagnose the relative activity of the disease. We must use modern care — rest in hospital, chemotherapy, education — and make sure that patients who have or have had tuberculosis are under medical observation throughout their lives.

Departments of health are our greatest hope. The law requires reporting of tuberculosis (by physicians, hospitals and laboratories). Health departments are required to find cases, plan care, and cooperate with physicians. They now have larger and better staffs than formerly and must make the most of their responsibility.

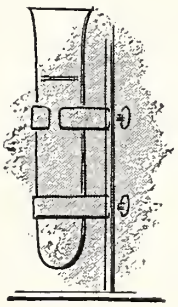
Volunteer associations for fighting tuberculosis must keep this disease as their major target. They must raise funds, publicize, educate, find cases and cooperate with physicians and health departments.

Sanatorium-hospitals must also do a better job of getting data, x-ray films and the like, and of planning and impressing upon the patient the importance of continued care.

Physicians must examine all patients with suspicious symptoms or lesions more thoroughly and often and forever for activity of disease. In cases of active disease by bacterial tests, treatment is mandatory. We must use chemoprophylaxis to prevent relapse. And we must bear in mind that certain conditions — peptic ulcer and operative treatment, diabetes, the use of steroid drugs, silicosis, known contact with tuberculosis — can lead to relapse.

A plan for care which could include a central registry (county or state), a central film storage, and card-carrying by patients would be a good but not infallible way of follow-up.

The time of diagnosis of many cases was in the wrong era; the knowledge concerning management was simply not at hand 20, or 10, or even 5 years. . . . Also, religious beliefs prevented medical care in two persons.



Biochemistry and Mental States

SEYMOUR S. KETY, M.D., *Boston*

THE SCIENCE OF neurochemistry has grown rapidly in the past decade or two. So great have been the contributions of biochemistry and molecular biology to understanding the chemistry of the brain that they could hardly be covered in the course of an evening's lecture. If we limit the review to those areas of biochemistry or neurochemistry which seem to have some relationship to mental state, we can more reasonably restrict the discussion. In fact, if we limit the review to those areas which have *definitely* been shown to have a relationship to mental state, I could probably stop now. However, it may be worth while to examine some provocative leads and areas of activity.

Consciousness

There are four aspects of mental state: consciousness, memory, thought processes and affect or mood. With regard to consciousness, some years ago I had the opportunity to work with Carl Schmidt, who interested me in the cerebral circulation and in the energy metabolism of the brain. We developed a method for examining these functions in man and applied them to a variety of conditions. To generalize very broadly from much of the work that went on ten or twenty years ago in a number of laboratories, I think it is fair to say that the energy metabolism of the brain does appear to have a crude relationship to consciousness.[3] That is, when the metabolism of the brain is interfered with in some general and rather serious way, there is a depression of consciousness, so that if one examines a variety of patients in coma of different etiologic background, one finds in general that the energy utilized by the brain has fallen to 70 or even to 40 percent of its normal value. This depression in oxygen consumption is also correlated with the depth of the coma (Table 1).

There are a number of conditions, however, in which there does not appear to be a correlation between oxygen consumption and the mental state. These include such conditions as schizophrenia, the performance of mental arithmetic, or the psychosis produced by LSD (Table 2). In a number of other conditions, even though there are serious disturbances in consciousness, the oxygen consumption of the brain cannot be distinguished from that of normal cerebral function. In sleep the metabolism of the brain is also not different from normal. This is a finding which was very interesting to us, because the older idea of sleep, which had been generated by Sherrington and by Pavlov, equated sleep with coma or anesthesia — that is, that sleep represented a generalized depression of the activity of the brain. In fact Sherrington, in one of the most poetic passages of his book, *Man on His Nature,* describing the sleeping and waking brain, made an analogy to the city at night with all of the lights out. As morning comes, a light goes on here and another one there, until the whole city is ablaze with activity. This had been the thinking about the state of the nervous system in sleep. We were therefore very surprised to find that in the sleeping state, the oxygen consumption of the brain was quite normal[9] so that sleep was different from coma or anesthesia. Sleep appeared to be more of a shifting of the circuits of activity in the brain than any overall depression. As you are undoubtedly aware, there has been described in the past ten years a new phase of sleep called paradoxical or activated sleep, or sleep with rapid eye movements (REM sleep). This form of sleep occurs in animals and in man, where it appears to be associated with dreaming.

REM sleep has interested physiologists ever since it was described by Dement and by Jouvet[6] but we still know very little about it. It is still an ex-

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TABLE 1.—*Reduced Cerebral Oxygen Consumption in Various States of Depression of Consciousness*

Condition	*Consumption Percent of Normal*
Senile psychosis	82
Diabetic acidosis	82
Insulin hypoglycemia	79
Artificial hypothermia	67
Surgical anesthesia	64
Insulin coma	58
Diabetic coma	52
Alcoholic coma	49

TABLE 2.—*Mental Conditions Not Correlated with Depressed Cerebral Oxygen Consumption*

Condition	*Consumption Percent of Normal or Control*
Normal sleep	97
Schizophrenia	100
LSD psychosis	101
Mental arithmetic	102
Anxiety	118
Epinephrine infusion	122

tremely mysterious phenomenon, but some of the things we have learned about it are remarkable. For example, in some recent studies with Evarts and Reivich, we have measured the regional blood flow of the brain in ordinary sleep and in rapid eye movement sleep, and have been thoroughly astonished to find that during the latter phase the blood flow to the brain is almost twice the normal value. There are very few conditions in which the metabolism of the brain is increased significantly, and practically nothing short of a convulsion will double the energy metabolism of the brain. Yet here is a phenomenon which is going on in all of us several times each night. Why this fantastic increase in blood flow during REM sleep occurs, I haven't the vaguest idea. I think it is probably in response to a comparable increase in oxygen utilization and metabolism, because other studies in California, by a group at UCLA,[2] have demonstrated a very sharp rise in brain temperature during REM sleep. This taken in association with the measurements of blood flow would be compatible with a pronounced increase in metabolism. This condition is still mysterious although we are learning a few more provocative things about it.

As everyone knows, there are many subtle things that go on in mental states that cannot be explained by the oxygen consumption alone. This is quite reasonable, for there are many things that happen to a radio or television set that cannot be explained by the power consumption. In the same way we would expect that other aspects of the chemistry of the brain would relate to more subtle aspects of mental state.

Memory

The next state that is worth mentioning, even if one does not engage in a long discussion, is memory. This has attracted the attention and interest of a number of scientists in the past five or six years, possibly because of the interesting findings of Hyden in Sweden about ten years ago.[8] He noted that in rats there were changes in the purine and pyridine base ratios of RNA in certain parts of the brain which appeared to correlate with learning. These data seem to have stood up in the hands of the few people who have tried to confirm them. From these interesting observations Hyden made a rather broad extrapolation to the hypothesis that just as genetic information is stored in the coding of the nucleotides in DNA, so the experimental information which the brain stores as memory was probably stored as sequences of amino acids or nucleotides in macromolecules in the brain. This hypothesis has attracted a great deal of attention and some support, although as a matter of fact I don't know of any firm evidence that supports it at the present time. There were some observations a year or two ago which suggested that when one trained rats to a particular task, one could then prepare an extract of the brain and inject it into other rats—naive rats —and in that way transmit the information. This, of course, if true, would have been very important evidence that memory was somehow stored as a chemical sequence in the macromolecule. Although the experiments have been repeated in many laboratories, in practically none has there been any evidence that a transfer of information actually took place. There are alternative explanations and none of them seem to support the idea that memory is literally transferred in this way.[10]

If we try to draw a generalization from much of the work in this field, I think the evidence does support the idea that protein synthesis may be crucial in the consolidation of memory — not so much in the acquisition of a learning experience, but in the ability of the brain to lay down that information into some permanent memory trace. I am referring now to a large number of experiments done by the Flexners, by Agranoff and by Barondes. They have used more or less specific inhibitors of protein synthesis injected into the brain of

a number of species at various stages during learning. Even though protein synthesis may be inhibited by 95 or 97 percent by some of these inhibitors, such as cyclohexamide or puromycin, the animal in most of these experiments continues to learn quite normally, but is unable to retain this information after several hours. I think it is a reasonable conclusion from much of this work that if one interferes with protein synthesis, one does in fact block the ability of the brain to consolidate memory.[1]

Now that, of course, is not proof that the memory is stored in the amino acid sequences of the protein, because the protein may be acting, and, in my own opinion, very probably is acting as a sort of solder, establishing new pathways or increasing the conductances of existing synapses. The memory may be stored in specific patterns in the network, the protein acting as a nonspecific solder necessary to establish these connections.

Thought Processes

If we move now to the third aspect of mental state, thought processes, I suppose the major disturbance of thinking which confronts us as physicians and especially confronts psychiatrists, is schizophrenia. This is a devastating disorder, and one in which thought processes seem to be involved. There has been a great deal of activity in the field of biochemistry as it relates to schizophrenia over the past ten or more years, in fact ever since physiological chemistry became a part of medicine and psychiatry. It is difficult to point with confidence to one area in all this activity which seems clearly to be leading to an understanding of the process of schizophrenia.[4] I don't mean to be negativistic or pessimistic, or to imply that this means that there is no biochemical aspect, but I cannot point to a particular area of biochemistry as being the most promising at the present time.

Let me mention some of the current hypotheses. Some 15 years ago a provocative hypothesis was developed by Osmond and Smythies, working with a biochemist in England, Harley-Mason. The interesting suggestion was made that the methyl group was probably involved in a number of biological processes that had to do with the catecholamines. It was predicted, in fact, that transmethylation, the adding of a methyl group, would turn out to be an important process in catecholamine metabolism. As a matter of fact, that prediction was confirmed more than ten years later by Axelrod, who showed, as I will indicate later, that methylation is one of the important ways in which epinephrine and norepinephrine are degraded in the body. Harley-Mason also pointed out, in conjunction with Smythies and Osmond, that a number of the psychotomimetic agents were methylated derivatives, especially mescaline, which was a very close analogue to dopamine, being essentially dopamine which had three methyl groups around the phenol ring. These men speculated that just as mescaline is an exogenous substance which produces a toxic psychosis, perhaps there was some abnormal metabolite of the catecholamines, a methylated metabolite, which produced the symptoms of schizophrenia, as a result of an internal toxin.

This is an interesting hypothesis, and in 1962 Pollin, Cardon and I, at the National Institute of Mental Health, had the occasion to test this hypothesis by giving methionine, which is a well recognized methyl donor and operates as such in many of the transmethylation processes in mammalian organisms. By giving large doses of methionine to some chronic schizophrenic persons, who had agreed to participate, and by giving a monamine oxidase inhibitor which would prevent the normal destruction of amines, we thought we would favor the conditions in which methylated amines could be produced, and see if they were produced in schizophrenic patients.

We also tested other hypotheses using other amino acids, and it was interesting that of some eight amino acids which we tested in this way, methionine was the only one that produced an intensification of the psychosis, and that in only a fraction of the schizophrenic subjects. Something like one-third of the patients whom we examined showed a decided intensification of psychosis with methionine. That was simply compatible with the transmethylation hypothesis; it by no means proved it. There are many reasons why methionine could be producing a toxic psychosis in schizophrenia, and we had by no means been sure that this was not a toxic psychosis superimposed on the schizophrenia. We have not been able, in fact, to convince ourselves that we can dissect that complex process from a true intensification of the schizophrenia *per se*. Nevertheless, the fact that methionine does intensify psychosis has been confirmed by a number of groups, and Himwich and his colleagues have shown that betaine, another methyl donor, will do the same thing. This lends further interesting support to the possibility that a trans-

methylation process has gone awry in schizophrenia.

Two years or so after those methionine experiments, Friedhoff reported finding in the urine of schizophrenic patients a substance which he identified as dimethoxyphenylethylamine (DMPEA). This is a remarkably interesting compound, and a number of us were very excited by this report because DMPEA is dopamine which is methoxylated in two positions as opposed to mescaline, the well-known hallucinogenic drug which is methoxylated in three positions. Thus DMPEA is two-thirds of the way toward mescaline; in fact it is the compound which Harley-Mason cited 12 years ago as being perhaps the most likely of the compounds that could be produced by transmethylation and cause schizophrenia!

This, of course, caused a great flurry of activity, and a number of laboratories rushed into the attempt to replicate Friedhoff's findings. The batting average varies from week to week. At the latest reading, many people have reported the finding of a "pink spot" in the urine of schizophrenic patients and not in the urine of normal persons. One of the best of these studies was done in Liverpool by Bourdillon, who took the precaution of having the examination of patients and urine done independently and blind. When he decoded the data, it was quite definitely demonstrated that in the patients who were clearly schizophrenic there was a high proportion in whom the pink spot was found. In those who were questionably schizophrenic a significant number yielded it, and in those who were not schizophrenic, the urine examination was negative with only one exception. The only difficulty is that Bourdillon did not control drug administration. The metabolites of the phenothiazines are notorious for persisting in the urine for weeks after the drug has been withdrawn, and for producing various colored spots in chromatograms of urine. As a matter of fact, there are two very convincing reports which have come from England in the past year in which the investigators seem to have proven quite well that the pink spot which is found in the urine of schizophrenic patients is not dimethoxyphenylethyamine at all. However, Friedhoff, in an analysis of gallons of urine from many patients with schizophenia, has isolated the material which he had previously identified chromatographically and, in a number of different assays demonstrated to his satisfaction that it is dimethoxyphenylethylamine. I think at the present time we cannot be sure, but the evidence is not conclusive that DMPEA excretion occurs in or is causally related to schizophrenia.

Another hypothesis in the etiology of schizophrenia was also advanced by Osmond and Smythies (later Hoffer joined them and Smythies left). It was postulated that in schizophrenia there was an abnormal metabolism of epinephrine which was transformed into a hallucinogenic agent, possibly adrenochrome. This hypothesis was widely promulgated for a number of years, to a large extent because it was difficult to test. No one knew anything about the normal metabolism of epinephrine, let alone its metabolism in schizophrenia. In order to test this hypothesis, we felt we needed some radioactive epinephrine of considerably greater activity than the C^{14}epinephrine which was then available. Epinephrine is such a powerful substance, and a safe dose is so small that a very high specific activity is required to carry out meaningful studies on its metabolic fate. This requirement was met with tritiated epinephrine of very high specific activity. With the help of this compound Axelrod very quickly worked out the metabolism of this amine. Now approximately 95 percent of its metabolic products can be accounted for (Chart 1). On the basis of this knowledge it was now possible to examine the metabolism of labeled epinephrine in schizophrenic patients. We found to our disappointment that the patients showed about the same patterns of metabolites of the administered epinephrine as did normal persons. No evidence of abnormal metabolites of catecholamines was found. Axelrod's work, however, prompted to some extent by the epinephrine hypothesis of schizophrenia, did lay the groundwork for knowledge of the metabolism of catecholamines in peripheral tissues and in the brain. This has been of immense subsequent usefulness.

Mood

I should like to turn now to neurochemical aspects of mood. This subject in my opinion is the most provocative and compelling area in the biochemical implications for psychiatry at the present time.[5] In a way this field can be said to have begun with the discovery of the psychotomimetic properties of lysergic acid diethylamide (LSD) more than 20 years ago. This substance, which has caused more than its share of social problems, has nonetheless been responsible for some important contributions to basic research, which we must not overlook. Next in the chain of seemingly unrelated

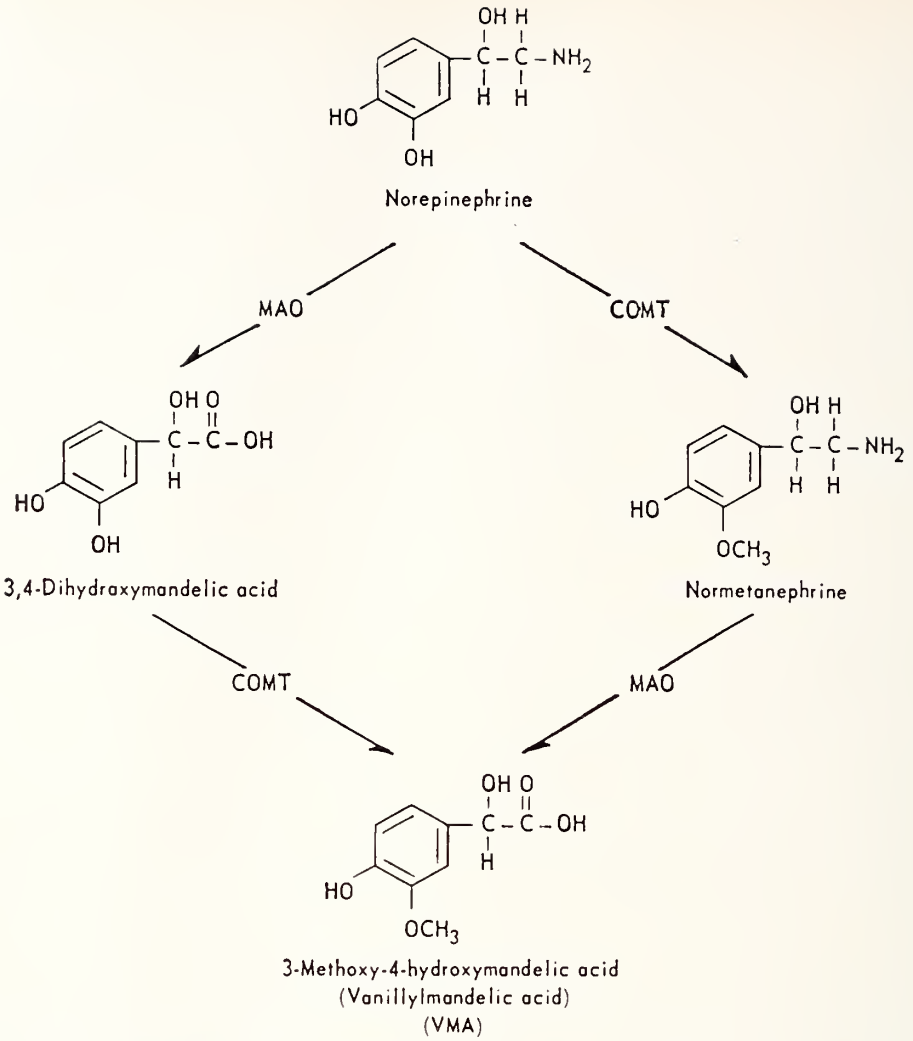


Chart 1.—Pathways of metabolism of norepinephrine (simplified). MAO, monoamine oxidase; COMT, catechol o-methyltransferase.

events was the discovery of a new biologically active amine by Rapport and Page in this country and by Erspamer in Italy, which the latter called enteramine and which in this country was called serotonin. It was found to be a simple indole amine, 5-hydroxytryptamine. Although highly concentrated in the gut, it was found in other parts of the body, especially in the brain. Here, it had a very interesting distribution. It was not uniformly dispersed, but was concentrated in the limbic system, in the hypothalamus, and in the brain stem that is, in the areas of the brain which neurophysiologists by that time had begun to suggest had something to do with emotional states. It was also known that serotonin affected smooth muscle. Then Gaddum in England and Wooley in this country made the very interesting finding that among the antagonists to serotonin, the best was LSD. This enabled both investigators to develop a rather interesting hypothesis that since LSD blocks the effect of serotonin on smooth muscle, and since serotonin is found in relatively high concentration in the brain, perhaps the reason that LSD produces psychosis is that it blocks the functions of serotonin in the brain. If that is the case, perhaps serotonin is necessary to keep us sane, and when something blocks, destroys or inhibits the serotonin in the brain, we become insane.

A few years later, iproniazid was introduced in the treatment of tuberculosis. It was found to be rather effective, as you remember, but it also produced a side effect of exhilaration. In fact, some of the first papers concerning the use of large amounts of this drug reported that the patients were dancing

in the halls of the sanitorium (and not because they had seen the x-ray report). They were dancing because iproniazid is a behaviorally activating drug. It was quickly learned that iproniazid was a monoamine oxidase inhibitor, and after its administration the concentration of serotonin in the brain rose appreciably. This was further evidence for Gaddum and Wooley's hypothesis.

There was also the finding that reserpine, the tranquilizing drug, also depleted serotonin in the brain. This further supported the hypothesis that serotonin played an important role in normal and abnormal mental states.

That simplistic explanation was very quickly challenged when shortly thereafter it was learned that a number of amines exist in the brain besides serotonin—norepinephrine and dopamine especially—and these amines are also affected by reserpine and iproniazid in much the same way as serotonin. It is fair to summarize a great deal of information by indicating that the activating effects of monoamine oxidase inhibitors and the depressant effects of reserpine and other congeners of reserpine appear to be related to the effects of these drugs upon one or more of these amines. We are not sure at the present time which specific amine is involved or whether all of them may not be involved in some very complicated way. However, the evidence since that time has tended to focus upon the norepinephrine in the brain. It exists there in high concentration, and there is considerable evidence that it is involved in mood and affect.

We have known since the time of Cannon that epinephrine has a great deal to do with the peripheral manifestations of anxiety, fear and rage. In recent years there has been an accumulation of evidence that central norepinephrine is equally involved in these affective states.[12]

Just before he died, Hillarp, the Swedish histochemist, developed a technique which was further pursued by his students, Dalhström and Fuxe, for demonstrating fairly specifically certain biogenic amines like norepinephrine, or serotonin in tissues. Their studies have revealed stores of norepinephrine in the vesicular nerve endings of certain neurons originating in the brain stem. The evidence is well established for particular neurons and tracts which seem to secrete norepinephrine, dopamine or serotonin. These neurons appear to have their cell bodies in the brain stem and to send axons throughout the brain, except for the dopamine-containing neurons which seem to be more localized to endings in the caudate nucleus.

A second technique which has contributed much to this field was devised by Gowinski and Axelrod, and is a means of labeling the norepinephrine in the brain by injecting tritiated norepinephrine into the cisterna magna or the lateral ventricle. These workers demonstrated that such labeled material quickly mixed with the endogenous pools of this amine in the brain, and could then be used to study its metabolism there.

As the result of work in the peripheral sympathetic nervous system, we can now picture a fairly good model of a sympathetic nerve ending. In these endings are a number of pre-synaptic vesicles which appear to contain norepinephrine. This overflows from the vesicles into the cytoplasm where it can be attacked by the monoamine oxidase which is in the mitochondria and is converted to the deaminated product. Some norepinephrine, and the functionally useful portion of it, eventually gets released from nerve endings into the synapse, where it acts on some ill-defined receptor in the postsynaptic cell and produces its effect. That norepinephrine can be O-methylated to form normetanephrine (NMN) or it can be taken up by some process which brings it back through the synaptic membranes into the axon (Chart 2).

To summarize considerable evidence, I think it is fair to say that every drug which has been found to affect mood, and which is useful in the treatment of depression, can be shown to have some action upon synaptic norepinephrine in the brain. For example, reserpine breaks the vesicular membranes in some way and releases the norepinephrine, but

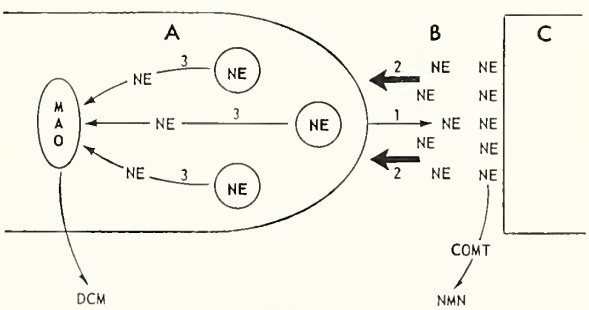


Chart 2.—Schematic diagram of (A) noradrenergic nerve ending, (B) synaptic cleft and (C) receptor. NE, norepinephrine; NMN, normetanephrine; DCM, deaminated catechol metabolites; COMT, catechol o-methyl transferase; MAO, monoamine oxidase (within a mitochondrion). 1, discharge of norepinephrine from nerve ending; 2, reuptake of norepinephrine from the synaptic cleft; 3, intracellular release of norepinephrine from vesicles to cytoplasm and to mitochondria. From Schildkraut and Kety.[12]

releases it presynaptically where it can be inactivated by the monoamine oxidase and released as a deaminated product. It never gets to the synapse and therefore diminishes the amount of effective norepinephrine. That may be why reserpine is a depressant agent. Monoamine oxidase inhibitors block that enzyme and increase the amount of norepinephrine available at the synapse. This can be inferred from the increase in normetanephrine which can be detected in the brain.

Amphetamine has a complex action, but among its effects are an inhibition of monoamine oxidase, a favoring of the release of norepinephrine at the synapse, an inhibition of its re-uptake, and perhaps an increased rate of synthesis, all of which would tend to increase the amount of norepinephrine acting at the synapse.

Finally, imipramine, which is very effective in the treatment of depression, doesn't block monoamine oxidase, and doesn't release norepinephrine, but has been shown recently to block the re-uptake of norepinephrine and therefore to increase the concentration of synaptic norepinephrine. Thus all these antidepressant drugs affect norepinephrine at central synapses in a way that would be compatible with the idea that this amine at the central synapses has something to do with mood.

Psychiatrists agree that electroshock is better than any of the drugs in the treatment of depression, yet there has never been a satisfactory explanation of how it acts. Last year at the Collège de France with Glowinski and a number of collaborators, we had an opportunity to tackle the problem of norepinephrine turnover in electroconvulsive shock.[7] We had found that in acute stress there is an increase in the turnover of norepinephrine in the brain, which we interpreted as indicating a greater release of the amine and a compensatory increase in its synthesis. We reasoned that since electroshock works for a prolonged period following the treatment, we would expect some persistent effect of electroshock upon norepinephrine synthesis in the brain. We did some experiments in which we subjected rats to electroconvulsive shock, twice a day for a week. When we examined the turnover of norepinephrine in the brains of these rats, 24 hours after the last shock, we found a 40 to 50 percent increase in turnover in the norepinephrine, suggesting a persistent augmentation in synthesis of this amine.

Thus electroconvulsive shock also takes its place with the anti-depressant drugs in favoring by one mechanism or another the availability of norepinephrine in the brain. This somehow lends credibility to the hypothesis that this amine in some way is involved in the depressive illnesses and in the beneficial effect of drugs and electroconvulsive shock. That is not to imply that it is the only amine involved or that depression can be explained by a decrease in brain norepinephrine. As in most psychiatric illness, the etiologic lineage is probably multifactorial and includes biological and genetic factors interacting with the powerful influences of life experience. But whatever the etiologic roots, it may be that in some of these illnesses biochemical factors form a crucial common path which can be changed to influence the clinical outcome.

REFERENCES

1. Agranoff, B. W.: Agents that block memory, *In* The Neurosciences, G. C. Quarton, et al.[11]

2. Kawamura, H., and Sawyer, C. H.: Elevation in brain temperature during paradoxical sleep, Science, 150, 912, 1965.

3. Kety, S. S.: Relationship between energy metabolism of the brain and functional activity, *In* Sleep and Altered States of Consciousness, S. S. Kety, et al.[6]

4. Kety, S. S.: Current biochemical approaches to schizophrenia, New Eng. J. Med., 276:325-331, 1967.

5. Kety, S. S.: The central physiological and pharmacological effects of the biogenic amines and their correlations with behavior, *In* The Neurosciences, G. C. Quarton, et al.[11]

6. Kety, S. S., Evarts, E. V., and Williams, H. L., Eds.: Sleep and Altered States of Consciousness, Res. Publ. Ass. Nerv. Ment. Dis., Vol. XLV, Williams and Wilkins Co., Baltimore, 1967.

7. Kety, S. S., Javoy, F., Thierry, A-M., Julou, L., and Glowinski, J.: A sustained effect of electroconvulsive shock on the turnover of norepinephrine in the central nervous system of the rat, Proc. Natl. Acad. Sci., 58:1249-1254, 1967.

8. Hyden, H.: Biochemical changes accompanying learning, *In* The Neurosciences, G. C. Quarton et al.[11]

9. Mangold, R., Sokoloff, L., Conner, E., Kleinerman, J., Therman, P. G., and Kety, S. S.: The effects of sleep and ack of sleep on the cerebral circulation and metabolism of normal young men, J. Clin. Invest. 34, 1092, 1955.

10 Quarton, G. C.: The enhancement of learning by drugs and the transfer of learning by macromolecules, *In* The Neurosciences, G. C. Quarton, et al.[11]

11. Quarton, G. C., Melnechuk, T., and Schmitt, F. O.: The Neurosciences, Rockefeller University Press, N. Y., 1967.

12. Schildkraut, J. J., and Kety, S. S.: Biogenic amines and emotion, Science, 156:21-30, 1967.

MEDICAL STAFF CONFERENCE

Diagnosis and Treatment of Salmonella Infections

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. EVANS*: The patient is a 67-year-old retired mechanic from San Salvador. He had been well until two years ago when he noticed progressively increasing shortness of breath on exertion and at rest, and swelling of the legs. Ten months before he was admitted to hospital he noted the occurrence of small indurated non-tender bruises which spontaneously resolved. Four days before entering the hospital he began to have constant, sharp, pleuritic chest pain. He became diaphoretic, and was comfortable only when sitting upright. It was in this condition that he was brought to the Emergency Room and admitted to the Intensive Care Unit.

On physical examination he was observed to be pale and obese and in acute respiratory distress. Blood pressure was 130/80 mm of mercury without pulsus paradoxus, the pulse rate 132, respirations 36, temperature 38°C orally. Pertinent physical findings included scattered lesions 1 to 5 cm in diameter with clear indurated centers and surrounding ecchymotic areas on the front of his legs and on his back. Jugular venous pulsation was visible 8 cm above the sternal notch when the patient was sitting at 90°. There was intercostal bulging, decreased breath sounds and dullness to percussion at both lung bases. The heart was not thought to be enlarged, but there was a prominent gallop and grade II/VI holosystolic murmur heard at the apex. There was pronounced pitting edema of both legs and sacrum. A few small, rubbery non-tender inguinal nodes were felt. The liver was palpable 5 cm below the left costal margin. The spleen was firm and diffusely enlarged without irregularity.

Laboratory examination on admission included an hematocrit of 27 percent and a leukocyte count of 233,000 per cu mm with 95 percent mature lymphocytes. Platelets numbered 105,000 per cu mm. The sedimentation rate was 80 mm in one hour. Urinalysis showed red blood cells, casts and bacteriuria. Culture of the urine grew out 2000 colonies of *Staphylococcus albus* per ml. Serum enzymes included a creatine phosphokinase of 10 units (normal 13 to 57), serum glutamic oxalacetic transaminase of 40 Karmen units (normal 8 to 40), lactic dehydrogenase of 600 units (normal 200 to 500 units). Serum uric acid was 9.6 mg per 100 ml and bilirubin was 1.7 mg (all direct reacting). Serum protein electrophoresis on admission was normal.

During his stay the patient was noted to have a rise in febrile agglutinins to both typhoid and typhoid 0. Skin tests were positive for mumps and negative for purified protein derivative.

He was treated with digitalis and diuretics, and his body weight decreased 16 kg while he was in

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hospital. During the first few weeks he had persistent fever of 38° to 39°C. Repeated blood cultures were negative for pathogens. Electrocardiograms taken on admission showed minor ST changes. Serial electrocardiograms revealed progressively decreasing voltage. The patient was seen by a cardiologist, who suggested the possibility of pericardial effusion. On the 19th day in hospital cardiac fluoroscopy showed decreased cardiac pulsations. At this time the peripheral venous pressure was 10 cm of water, and circulation time was 10 seconds. Four days later, pericardiocentesis was performed and 40 ml of serosanguinous fluid was withdrawn. It had an hematocrit of 5 percent and contained 29,100 leukocytes per cu mm, of which 35 percent were neutrophils. At the same time 95 to 96 percent of the peripheral leukocytes were lymphocytes.

Culture of the pericardial fluid grew gram-negative rods, which were subsequently identified as *Salmonella typhimurium*. A course of kanamycin and ampicillin was begun. In the two weeks after this treatment was begun the patient showed decided improvement in clinical status and became afebrile.

He was discharged on the 48th hospital day. Leukocytes at that time numbered 164,000 per cu mm. 96 percent of which were lymphocytes. Ampicillin, isoniazid and prednisone were being administered at the time of discharge.

DR. JAMES YOUKER*[1]: The chest film taken at the time of admission shows a calcified density in the right superior mediastinum. The heart is enlarged (Figure 1). On each side there are pleural effusions, and on the right side there is an area of collapse, which is present on some subsequent films, and not on others. The heart shadow did not change significantly after pericardiocentesis. We still see the pleural effusions. The cardiac shape is that of the "water bottle" heart, characteristic of pericardial effusions.

DR. SMITH*[2]: We are very pleased to hear how well he has been doing. This patient has, of course, a very complex series of difficulties involving a number of organ systems. This morning we are going to concentrate on only one aspect of his illness: that of presumed salmonella infection. We are very pleased to have as a discussant Dr. Stephen N. Cohen. I would like to introduce Dr. Cohen

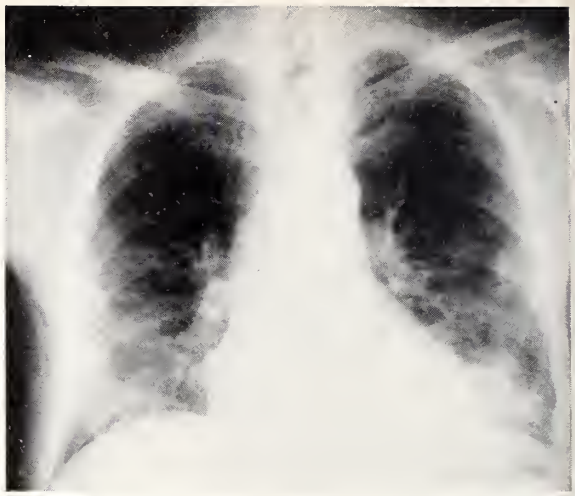


Figure 1.—X-ray film of chest taken shortly after patient entered the hospital.

to this audience. He is a graduate of MIT and then of Harvard Medical School, received his internship and residency at Boston City Hospital on the Thorndike Service. He spent two years at the Communicable Disease Center in Atlanta and returned as a Fellow in Infectious Disease with Dr. Edward Kass at the Boston City Hospital. He now has joined the faculty here in the Division of Clinical Pathology where he will be in charge of the diagnostic bacteriological laboratories.

DR. COHEN*[3]: Thank you very much, Dr. Smith. Three aspects of this patient's illness must be considered: Salmonella infection, the relation of that infection to the underlying disease and defective immune capabilities, and the general problem of acute purulent pericarditis. This latter subject, as Dr. Smith has implied, is probably a sufficient subject for a separate conference, and I shall concentrate on a discussion of salmonellosis.

There has been an enormous increase in recorded cases of salmonellosis in recent years. The number of cases has risen from 700 in 1946 to over 20,000 in 1965, at the same time that reported cases of typhoid fever, a more serious and better-reported illness, have decreased by 80 percent. Part of this increase no doubt reflects more effective culture techniques. These techniques are more widely used since the availability of specific antibiotic therapy has made specific diagnosis more necessary.

At one time salmonella infections were considered to be of sporadic and local origin. With more

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information this assumption has been proved false. Taking advantage of minor structural differences in the biochemical composition of cell walls and appendages of the enteric Gram-negative bacteria, scientists have been able to identify over 800 individual members of this genus. The use of this precise identification, combined with centralized tabulation of reported cases, has revealed the existence of recurrent interstate and intrastate epidemics. Many of these epidemics have been of large size. The sources have been contamination of various household items, particularly processed foods.

A wide variety of foods, especially poultry and poultry products including frozen and powdered eggs, has been incriminated in outbreaks in recent years. In addition, various animal species which are found in the home have also been incriminated in localized episodes of salmonellosis. Of special interest to a medical audience is the fact that salmonellae have been recovered at times from therapeutic materials such as vitamin tablets, yeast extract, gelatin, pancreatic extracts, pituitary substance and thyroid preparations. One year ago, this hospital and several others in the United States and abroad shared an unpleasant experience: 37 known cases of salmonellosis arose from the diagnostic administration of carmine red dye. One of the patients died. The dye, which is used as a marker for intestinal transit time, was contaminated with *Salmonella cubana.*

In the past few years a large proportion of reported cases have appeared to be acquired by patients in hospitals. In 1964, Hook[5] found 65 reports of hospital outbreaks of salmonellosis over the previous period of 35 years. He excluded typhoid transmitted in hospital. Since that time the number of reports has probably doubled, with additional reports of hospital outbreaks occurring nearly every month. The largest outbreak involved a thousand reported cases. It occurred mainly in the northeastern United States and involved *Salmonella derby.* During that outbreak, the frequency of isolation of this relatively obscure organism rose from 2 percent to nearly 15 percent of all reported salmonella isolates, and to 30 percent of the isolates in the Northeast. The epidemic was associated with several deaths. Intensive surveillance at one Philadelphia hospital revealed over 350 cases, of which one-third were asymptomatic. There are some interesting lessons in the experience at that hospital. Policemen were stationed in the halls to enforce a rigid isolation policy and to prevent unauthorized persons moving between wards. Despite a decided fall in the incidence of staphylococcal infection, no effect upon the incidence of new cases of salmonellosis could be seen.

There are many reasons why hospitals may be favorable environments for epidemics of salmonellosis: Most important, they admit patients with salmonella gastroenteritis who serve as a source for spread of the disease, and they house a number of debilitated patients. The importance of debility in host resistance is always a very difficult one to document, but I will just add my "clinical impression" that sick people tend to have more severe infection when salmonellosis develops. A number of other factors may play roles in such epidemics. For example, decreased intestinal motility brought about by giving opium to a guinea pig causes much higher salmonella counts in the intestine, earlier systemic invasion by the microorganism and earlier death. Hospitals have many patients who have decreased intestinal motility resulting from infections, gastrointestinal procedures and the like. Another factor which cannot be neglected is the increased efficiency of diagnosis in a hospital. It is obvious that in a hospital the cause of 100 cases of diarrhea is more likely to be determined than is that of diarrhea in 100 diners in a restaurant who go home to their separate corners of the city and have their illness in relative solitude. Cultures are more readily obtainable in a hospital.

Unfortunately such items as enema cans, whether used with barium or for other purposes, have been found to be sources of infection in some hospital epidemics. Gastrectomy has been reported to be associated with unusual risk of salmonella infection. Meynell has shown that gastric fluid at pH 2 will almost instantly kill 99 percent of salmonella, whereas when the pH is 3, virtually all survive. This may be an important barrier to the entrance of salmonella into the intestinal tract. The use of raw eggnogs in tube feedings has been associated with a large number of cases. Such feedings have been proscribed in many hospitals.

Finally, immunosuppressants, steroids and antimetabolites may increase susceptibility to this infection as well as to other infections. An interesting decade of experimental work has apparently elucidated an association which had been known for some time previously—the ability of antibiotics

to predispose to infection with salmonellae. Antibiotics generally decrease the number of aerobes in the intestinal tract, and the loss of their metabolic activity may make the environment less favorable for growth of anaerobes. Anaerobes and not *E. coli* are the dominant flora of the intestinal tract, and are responsible for the production of large amounts of short-chain fatty acids which have been found in feces in concentrations adequate to yield *in vitro* inhibition of salmonellae.

Certain aspects of the epidemiology of salmonella infections are of interest. The peak incidence of infections occurs in July and August. Presumably food is least well refrigerated during the summer months. Clinically significant salmonellosis typically affects patients at both extremes of age. The presumed explanation for the concentration of cases among the youngest children is lack of immunity, since the major antibodies to Gram-negative organisms, 19-S antibodies, are not transmitted across the placenta. Some degree of immunity to salmonellae must be acquired during the first year or two of life. At the other extreme of age there is another increase in incidence, presumably reflecting the increasing numbers of patients with debilitating illnesses such as the one under discussion today.

Salmonella infection occurs in some combination of four major patterns. The first is the asymptomatic carrier state. It may be present without a recognizable symptomatic period or may precede or follow one of the other patterns. Probably most infections are asymptomatic, with some 0.5 to 2 percent of people infected at any given point in time.

The next largest clinical group is composed of patients with gastroenteritis. Symptoms usually develop within 12 to 72 hours of oral exposure, but incubation periods of up to two weeks have been reported. Symptoms include abdominal pain, diarrhea, and fever. Patients with gastroenteritis make up 50 to 70 percent of the series of 8,000 patients with salmonellosis collected by Saphra and Winter.[10] It is likely that transient bacteremia is a frequent but often undiagnosed complication of *Salmonella typhimurium*. This organism, isolated in the patient under discussion this morning, usually produces the gastroenteritis pattern, and is responsible for about one-third of all the salmonella isolates reported in the United States.

The third pattern is that of enteric fever, and approximately ten percent of cases of clinical salmonellosis are of this order. Enteric fevers may be defined as blood-borne infections without signs of focal collections of pus. Frequently blood cultures are positive when stool cultures are negative.

The fourth pattern is that of focal infection. Bacteremia may be so mild or so transient as to pass unnoticed. This must have been the situation in the present case. The patient gave no history of illness suggestive of septicemia but had well-established focal infection when first seen. Focal infection most commonly occurs in bone, meninges, walls of arteries, the endocardium, or in tumors. The infection may present almost anywhere (for example, the pericardial localization in the present case).

Certain disease processes seem to increase susceptibility to systemic salmonellosis. Patients with sickle cell disease and its variants have long been known to have an unusually high risk of salmonella osteomyelitis. The mechanism of this association is obscure. The patient today illustrates another important group of diseases associated with severe salmonellosis and focal infection. A recently reported study from Roswell Park[4] discusses the incidence of salmonellosis in disseminated malignant disease. It is difficult to draw any firm etiologic conclusions from these data because of multiple variables: malignant disease and treatment with steroids and antimetabolites. In a seven-year period clinically important salmonellosis developed in one of every 140 patients with leukemia or lymphoma. This incidence may be compared to one in 2,800 patients with carcinoma or one in 9,200 patients without malignant disease. Patients with rectal and pelvic carcinoma have a higher incidence of salmonellosis (one in 600) which might be explained by the effects of a direct surgical insult upon persisting asymptomatic infection. An observation of some interest is that 70 percent of patients with salmonella bacteremia had lymphoproliferative disorders.

Although in the present case the proportion of polymorphonuclear cells in the total number of leukocytes was very low—only 5 percent—the absolute number of neutrophils was greater than 10,000 per cu mm, a number adequate to protect against excessive risk of infection. What, then, is the basis for the apparent susceptibility of patients with lymphoproliferative disorders to salmonella infection? There are currently two major schools of thought as to the mechanism of immunity to this organism. One explanation is largely based

on studies in mice with *Salmonella typhimurium* and other salmonella species. Jenkin and Rowley have expressed belief that humoral antibodies of the 19-S globulin variety are bound to macrophages and facilitate the destruction of the bacteria ingested by these macrophages.[7] Such cells containing this tightly-bound antibody and free of circulating antibody are capable of transferring resistance to salmonellae to non-immunized animals. This work has been substantiated by Japanese workers who appear to have successfully isolated the cell-bound antibody.[8] The other major hypothesis has been best developed by Mackaness and his colleagues,[1] who agree that macrophages from infected animals have increased bactericidal activity against salmonellae, but hold that this activity is nonspecific and unrelated to humoral antibody. For example, they find that infection with *Listeria* protects against superinfection with salmonellae and vice versa. Mackaness expressed belief that delayed hypersensitivity mechanisms are probably more important than humoral antibody in recovery from salmonella infections. The debate will obviously not be settled here this morning, but we must note the very recent report that listeriosis is an infection found with unusual frequency in patients with malignant disease. Of 18 patients with listeriosis observed by Louria[9] during an 11-year period, 16 had lymphoproliferative disorders.

In the present case tests were done to evaluate the patient's immune status. He reacted to mumps antigen with delayed skin hypersensitivity. Patients with lymphoproliferative disorders frequently are unable to respond to primary antigenic stimulation with either humoral or delayed hypersensitivity. The electrophoresis of the patient's serum was normal, as were total levels of gamma globulin. It would have been interesting to know the results of an immuno-electrophoresis of serum as well, and whether the patient would respond to primary antigenic stimulants of delayed hypersensitivity such as dinitrochlorobenzene.

There is little doubt now that the patient entered the hospital with acute purulent pericarditis. Accurate figures for the incidence of acute purulent pericarditis do not exist, but Boyle and coworkers[2] found an incidence of 0.1 percent at autopsy. It is clearly an uncommon illness, but it accounts for about 10 percent of acute pericarditis of all types. Most cases of purulent pericarditis arise from bacteremic infection or from direct extension from pneumonia or empyema. Less common causes include penetrating wounds of the pericardium, perforation through the diaphragm of a subdiaphragmatic abscess, or perforation of an infected heart valve into the pericardium. Accordingly, the commonest organisms found in the review by Boyle were staphylococci, pneumococci, streptococci and meningococci. There are organisms found frequently in either the blood or in the lungs. The incidence of pneumococcal, streptococcal, and meningococcal pericarditis has fallen decidedly since the advent of antibiotics, and we may expect that less common and more resistant organisms will now make up a larger proportion of the cases.

Eight cases of salmonella pericarditis were reported up to 1961; three of them were due to *Salmonella typhimurium*. Two of these illnesses ended in death. In two patients who died the diagnosis was unsuspected during life. There are no features unique to salmonella pericarditis, although one should suspect this agent in pericarditis accompanying or following diarrhea.

The classic symptoms of pericarditis include sharp, anginal or less commonly pleuritic or central chest pain, which causes the patient to breathe shallowly and rapidly and to sit up and lean forward. (It is interesting that in the present case the patient is described at the time of admission to hospital as "sitting bolt upright." Of course, he had another reason to be sitting bolt upright—the orthopnea resulting from 20 kg of fluid retention.) Fever and toxicity are usually present, sometimes with shaking chills, and may be so severe as to overshadow the focal signs. Hiccups may suggest involvement of the diaphragmatic pleura, and cough may be prominent. Physical examination may reveal a large area of cardiac dullness, diminished intensity of cardiac sounds, signs of congestive failure if venous return is sufficiently embarrassed or if myocarditis is present, and, most definitively, a pericardial or pleuropericardial friction rub (which did not develop at any time in the present case). The electrocardiogram may show diminished height of QRS complexes, or may show very elevated ST segments. X-ray and fluoroscopic studies may show an enlarged cardiac shadow with poor pulsations. Dye, carbon dioxide contrast or echocardiographic studies may show a cardiac wall of excessive thickness. The classic signs and symptoms may be entirely absent, however, except for fever. This latter may be only low grade or

intermittent, especially if antibiotics have been given.

In the present case many of these findings were present on admission, but not enough to definitely establish the diagnosis. When decreased electrocardiographic voltage in the QRS complexes developed, the diagnosis of pericarditis was quickly suspected. After fluoroscopy demonstrated decreased cardiac pulsations, pericardiocentesis was mandatory. Six days elapsed after effusion was diagnosed before aspiration was attempted in this case, because the patient was felt to be too ill to withstand the procedure. I think that this reluctance can be debated.

Once pericardial effusion is detected, the fluid must be examined to exclude the possibility of pyogenic or tuberculous pericarditis, although in this particular case leukemic infiltration of the pericardium was certainly under consideration. In otherwise normal patients with purulent pericarditis, essentially 100 percent of the cells are polymorphonuclear neutrophils. Examination of Gram stained or acid-fast stained exudate will usually reveal the causative bacteria. In the patient under discussion, only 30 percent of the exudate cells were neutrophils. This figure reflects a significant increase above the percentage of neutrophils in the peripheral blood, but that observation could not definitely establish the existence of bacterial pericarditis. The absence of bacteria in the Gram stained pericardial exudate is surprising. Considering how well the patient was tolerating the infection, it seems possible that his defense mechanisms were functioning at a low level and that he was successfully circumscribing the infection with the result that the number of organisms was too low to be seen on a smear.

In cases where purulent pericarditis is the presumptive diagnosis a rationally chosen antibiotic may be directly placed in the pericardial sac. Because of the predominance of the Gram-positive organisms as etiologic agents, the drug of choice will usually be penicillin or methicillin. What information is available suggests that antibiotics will penetrate into the pericardial sac when they are given systemically in high dosage; however, they certainly will not reach as high a level as can be obtained with direct irrigation. Furthermore, the acidity of highly purulent exudates may interfere *in vivo* with the bactericidal effect of some antibiotics, particularly the aminoglycosides such as streptomycin or kanamycin, which the patient in the present case received. Thus there are a number of reasons for introducing antibiotics directly into the affected space.

The importance of selecting a bactericidal antibiotic over a so-called "static" antibiotic is generally a pretty debatable issue, but in this case with a presumed impairment of immune defenses there is no disagreement that the penicillins, the aminoglycosides and the polymyxins are the most satisfactory drugs.

The results of treatment in salmonella pericarditis are too few to be analyzed, although the few recorded results appear to be quite good. No adequate experience with purulent pericarditis can be assembled from any one medical center, and it is therefore necessary to compare series obtained at different times and in different ways. In series in which the best results at the present are reported, the mortality is still about 20 percent. This mortality may in part be due to the frequent delay in diagnosis. It has been estimated that in 70 percent of cases the diagnosis has been completely missed during life.

There is no evidence for chronic constrictive pericarditis arising from the acute purulent infections. Therefore the physician is not forced to immediately consider open surgical drainage of the infected space. The published results are not such as to permit comparison of open surgical drainage and antibiotics on the one hand with closed irrigation and antibiotics on the other. The most reasonable approach can probably be developed by examining the experience with the treatment of acute bacterial empyema. Where little pus is present and where the organism is quite sensitive to antibiotics—as, for example, the pneumococcus—repeated aspiration (at least until the fluid is known to be sterile) combined with local and systemic antibiotic therapy, will usually be adequate. Where there is question of loculation of fluid and where the drainage is thought to be inadequate, where thick pus is present, or where the organism is insensitive, and in any case where the patient fails to show a rapid clinical improvement, open surgical drainage is mandatory.

The usual sensitivity pattern obtained with salmonella species, especially when the organism is acquired outside the hospital, indicates that the organism is sensitive to nearly every antibiotic. Despite these *in vitro* results, however, the clinical response is often extremely poor. It is not uncommon for patients to have positive blood cultures or

stool cultures during the administration of antibiotics to which the organism is sensitive *in vitro*. Nor is it uncommon to find a patient with negative cultures relapsing as soon as treatment is stopped. In such a case the organism usually retains the original sensitivity pattern. This phenomenon of antibiotic failure is not understood. It was at first ascribed to protection of organisms inside the macrophages where the antibiotics were thought not to penetrate. Recent evidence suggests that the drugs do in fact enter the cells, and that their failure may be related to the metabolic inactivity of the infecting organism inside the macrophage. An excellent example of the inefficacy of antibiotics was an English study of the treatment of intestinal salmonellosis.[3] The frequency of a prolonged carrier state in a group of children with fecal salmonellosis who were given antibiotics was double that of a group of similarly affected children who were allowed to recover from salmonellosis without the administration of antibiotics.

There is a general consensus that the fecal carrier state is untouched by antibiotics. Although antibiotics have been shown to be useful in typhoid fever, there is no evidence that they are of help, and there are many cases in which they have failed in systemic non-typhoidal salmonellosis. Nonetheless, there is little else we can offer to severely ill patients with systemic salmonellosis, and antibiotics are often given in the hope of possible benefit. Ampicillin or chloramphenicol are usually considered the drugs of choice.

One last point I would like to discuss is the use of so-called "febrile agglutinins" in the diagnosis of salmonellosis. I feel very strongly that these tests are virtually useless. In a country where typhoid fever is an unusual disease, and where the incidence of false positives is higher than the incidence of the disease, there is very little use for this test. The basis for false positive tests lies in the widespread sharing of antigens between typhoid and the other salmonellae and ubiquitous organisms such as *E. coli*. On the other hand, a significant proportion of patients with typhoid, and a much larger proportion of patients with salmonellosis other than typhoid, never have febrile agglutinins. When a test must always be checked by cultural results, I think it is fair to say we should abandon it and stick to cultures.

A PHYSICIAN: Would you comment on the effectiveness of vaccination?

DR. COHEN: First we must decide whether we are talking about typhoid or other salmonellosis. The use of typhoid vaccine dates back to at least World War I, but it was only about ten years ago that typhoid vaccination was shown to be effective. It is effective if the proper vaccine is used. The vaccine gives at least partial protection against typhoid, although this can be overwhelmed by a massive exposure. I should point out that although triple vaccine, so-called TAB vaccine, is generally available, no one has ever shown that the AB components of the vaccine have any useful effect. At least one public health department [Massachusetts] has stopped distributing it, both because of the fact that paratyphoid A is not common—there is an average of ten cases per year reported in this country among 20,000 salmonella isolates—and because efficacy of the vaccine has never been shown.

DR. SMITH: Studies in prisoner volunteers by Hornick, Woodward and their collaborators have pointed out that typhoid vaccine gives protection against small inocula of salmonella typhosa but not against more massive exposures.[6]

QUESTION: What about carriers of salmonella?

DR. COHEN: We must first distinguish permanent from transient carrier status. Convalescent carrier status can last for two to three years in some kinds of salmonellosis, so we do not usually get upset until some time has passed. Permanent carriage with salmonellosis other than *S. typhi* is unusual. It is probably somewhere around 0.5 percent or less, as compared with 3 percent with typhosa. There is no clear guideline about what to do with such patients. For typhoid it has been thought that once a patient was known to be a carrier he remained a carrier. About half of the carriers who have had gallstones have been cured of their infection by cholecystectomy, the other half continuing to harbor their typhoid elsewhere. Surgical intervention was the only known means of terminating the carrier state until a few years ago when English workers and later Simon and Miller at Stanford[11] showed that a significant proportion of permanent typhoid carriers could be cured by long-term, massive therapy with ampicillin. This is still imperfect treatment. Simon produced negative cultures over a follow-up period of a year. On the other hand excretion of organisms is irregular in typhoid, and it may take years to find out if the

antibiotic has really worked. I think no solid recommendation can be made.

DR. SMITH: In other words, "Salmonella Mary" will still be with us.

REFERENCES

1. Blanden, R. V., Mackaness, G. B., and Collins, F. M.: Mechanisms of acquired resistance in mouse typhoid, J. Exper. Med., 124:585-600, 1966.

2. Boyle, J. D., Pearce, M. L., and Guze, L. B.: Purulent pericarditis: Review of literature and report of eleven cases, Medicine, 40:119-144, 1961.

3. Dixson, J. M. S.: Effect of antibiotic treatment on duration of excretion of *Salmonella typhimurium* by children. Brit. Med. J., 2:1343-1345, 1965.

4. Han, Tin, Sokal, J. E., and Neter, E.: Salmonellosis in disseminated malignant diseases—A seven-year review (1959-1965), New Eng. J. Med., 276:1045-1052, 1967.

5. Hook, E. W., and Kaye, D.: Hospital-Associated Salmonellosis, *In* Proceedings: National Conference On Salmonellosis, Mar. 11-13, 1964, PHS Publication No. 1262, Mar. 1965, pp. 47-50.

6. Hormek, R. B., Woodward, T. E., McCrumb, F. R., Snyder, M. J., Dawkins, A. T., Bulkeley, J. T., De La Macorra, F., and Corozza, F. A.: Study of induced typhoid fever in man—Evaluation of vaccine effectiveness, Trans. Ass. Am. Phys., 79:361, 1966.

7. Jenkin, C. R., and Rowley, D.: Basis for immunity to typhoid in mice and the question of "cellular immunity," Bac. Rev., 27:391-404, 1963.

8. Kurashige, S., Osawa, N., Kawakami, M., and Mitsuhashi, S.: Experimental salmonellosis—X cellular immunity and its antibody in mouse mononuclear phagocytes, J. Bac., 94:902-906, 1967.

9. Louria, D. B., Hensle, T., Armstrong, D., Collins, H. S., Blevins, A., Krugman, D., and Buse, M.: Listeriosis complicating malignant disease—A new association, Ann. Intern. Med. 67:261-281, 1967.

10. Saphra, I., and Winter, J. W.: Clinical Manifestations of Salmonellosis in Man, New Eng. J. Med., 256:1128-1134, 1957.

11. Simon, H. J., and Miller, R. C.: Ampicillin in the treatment of chronic typhoid carriers, New Eng. J. Med., 274:807-815, 1966.

CORRECTION

The title of the case report by Drs. Samuel A. Weisman and Phillip C. Shiu in the April issue of CALIFORNIA MEDICINE (page 308) was correct except for one large detail: a question mark was omitted. The title should have been: "Hypothyroidism and Infectious Mononucleosis — An Unusual Association?"

CASE REPORTS

Hereditary Osteo-Onycho-Dysplasia—The Nail-Patella Syndrome

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HEREDITARY osteo-onycho-dysplasia or HOOD (nail-patella syndrome) consists of a group of hereditary anomalies primarily affecting the nails, elbows, pelvis and knees. Although considered rare, the condition may be more common than is realized. Patients are frequently treated for a single feature without recognition of the entire syndrome.[6] Most patients are asymptomatic, the anomalies being found after medical advice was sought for unrelated conditions[2] and a history and examination of the patient's family reveals others affected with the syndrome.

The recent examination of two patients with HOOD and their families prompted this report, with attention to salient features that may lead to early diagnosis. A further item of the report is the relatively recent awareness of nephropathy in this syndrome.

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Submitted 18 December 1967.
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Features of HOOD

Nails

Nail dystrophy is the commonest feature of HOOD, with an incidence of 93[4] and 98[2] percent reported in large series. In any case in which dystrophy of nails occurred, thumbnails were always affected, with other nails less frequently and less severely involved. The changes may include the toenails.

The spectrum of abnormalities may vary from slight longitudinal ridging to complete absence of a nail. Usual changes consist of hypoplasia, thinning and longitudinal ridging. In many instances nails are split in two by a longitudinal cleft and the lunules are poorly formed.[2] Abnormalities are symmetrical and persist throughout life. Nail-patella syndrome may be diagnosed at birth from nail changes.[14]

Knees

Knee changes occur in approximately 90 percent of cases.[2,4] The vast majority of patients have patellar hypoplasia, although absence, subluxation and dislocation are also prominent features. The shape of the hypoplastic patella may be ovoid, triangular or irregular.

The medial femoral condyle is frequently large and the lateral small. The tibiae may rotate laterally. Frequently the patellar tendons are lax.

The patella may be subluxated or completely dislocated. Recurrent dislocation may be a serious problem and it appears to be the major reason patients seek medical advice for the nail-patella syndrome. The tendency for the patella to dislocate laterally may produce a considerable walking impediment, particularly walking downstairs. Early osteoarthritis frequently occurs. Affected infants may be slow to walk and have an abnormal gait.

Elbows

Elbows are involved about as commonly as the knees—that is, in 90 percent of patients.[2,4]

The essential feature is hypoplasia of the lateral side of the joint. The carrying angle is frequently increased and there may be an enlargement of the medial epicondyle. Hypoplasia involves the radial head particularly, but may involve the capitellum and lateral epicondyle also.

The radial head may articulate normally with the capitellum but may be subluxated or completely dislocated. Changes, unlike those of nail dystrophy, may be asymmetrical. Dislocation is nearly always posterolateral and if it is complete the radial head is small and rounded and the neck elongated and narrowed. Mild to moderately severe impairment of extension, pronation and supination of the forearm may be present.[14]

Pelvis

"Iliac horns" are the pathognomonic feature of this syndrome, but they are not always present. Since these harmless functionless bony projections are obscured they are frequently overlooked, and this is reflected in the low incidence of this finding in some series. Careful evaluation has revealed iliac horns in 87 percent[2] of cases of HOOD.

Iliac horns arise from the posterior aspects of the ilii. Each may have an epiphysis-like cap or secondary center of ossification at its tip. They vary from a faint sclerotic line to 4 cm in length. They frequently are easily palpable and are sometimes visible. They are invariably bilateral and usually symmetrical. They are present as early as six months of age.

Flaring of the iliac crests has been reported[4] with the pelvis assuming a winged appearance likened by Lacroux[13] to elephant ears.

Associated Anomalies

Nephropathic Changes

Renal dysplasia appears to be an infrequent but potentially fatal component of the nail-patella syndrome. Hawkins and Smith[8] are credited with the first reports of kidney dysfunction in HOOD when they reported a family in which the propositus had died and changes typical of chronic glomerulonephritis noted at autopsy. The grandmother of the propositus had died of "dropsy" and his uncle and brother had albuminuria.

"Chronic glomerulonephritis" was reported on autopsy of another patient with HOOD who died at age 26 of nephritis.[1] Jameson, Lawler and Renwick[9] also report cases of "Bright's disease," "chronic nephritis," "chronic glomerulonephritis" and "chronic albuminuria." A 20-year-old woman with HOOD and a nephrosis-like clinical course, had focal glomerulonecrosis and diffuse tubular degeneration of the kidneys.[7] Muth[15] studied another patient who had a complete renal evaluation including percutaneous renal biopsy, because of persistent proteinuria. Eighty percent of the glomeruli in the biopsy specimen had mainly minor changes consisting for the most part of small areas of endothelial and epithelial cell proliferation.

Carbonara and Alpert in 1964[2] reviewed cases of HOOD in the American literature since 1948. They found proteinuria present in 42 percent of cases in which urinalysis was mentioned.

Iris Pigmentation

A defect in the iris reported in patients with HOOD consists of an outer zone of pale pigment and an inner zone of dark coloration arranged like a cloverleaf[3,11] ("Lester's sign"). Cosack[3] reported this anomaly in family members unaffected by HOOD, and this is related to another gene, which may be linked with other sporadic anomalies to the nail patella syndrome.[2]

Infrequent Anomalies

Small incidences of other defects have been reported, including mental deficiency, postural changes, and wrist and shoulder abnormalities, which appear to be coincidental.

Metabolic studies have revealed excessive urinary excretion of acid mucopolysaccharides. This change is not specific and has been seen in other generalized skeletal disorders.[2,12]

Genetic Studies

HOOD is transmitted as a non-sex linked dominant character. All affected persons have an affected parent. Complete transmission of the trait has been reported through six successive generations.[5] Since genes are paired, one would expect a parent with this dominant trait to pass it on to half his offspring, and large studies bear this out.[5]

The gene expresses itself variably, the nail changes almost always being present with various combinations of elbow, pelvic and knee involvement.

Lawler, Renwick and coworkers[10,16] have shown that the responsible gene lies on the same chromosome as the ABO blood group locus. In any given family the gene for the syndrome will be transmitted in association with only one of the genes of A, B or O.

Case Report and Family Survey

CASE 1.—A 15-year-old girl was admitted to St. Joseph Hospital on 19 September 1966 because of pain in the right lower quadrant of the abdomen. In June 1966, this patient had been seen because of a urinary tract infection and she received uroseptic drugs for one month.

Because of the abdominal pain, abdominal films were obtained. They demonstrated well developed iliac horns (Figure 1). The patient also had the remainder of the classic tetrad—dysplastic nails, radial head subluxation (Figure 2), and rudimentary patellae (Figure 3).

Results of routine laboratory tests, an intravenous pyelogram and a lower gastrointestinal series were all within limits of normal. The patient's symptoms subsided and she was discharged.

This patient is the only one of four siblings with the syndrome. The propositus mother has involvement of nails, knees and elbows; and she is the only one of three siblings with any involvement. The maternal grandmother has the same involvement and of three siblings is the only one affected.

The next two preceding generations affected involved the maternal great grandfather and great-great grandfather, and it was known that in them the nails and the knees were affected.



Figure 1.—(Case 1) Classic example of bilateral iliac horns seen on abdominal survey before barium enema study.

CASE 2.—A 16-year-old girl was first admitted to the Orthopedic Service of St. Joseph Hospital 1 July 1966 on complaint of a knobby appearance of the elbows. Physical examination revealed bilateral radial head disclocation, with minus 10 degrees of supination in both elbows (Figure 4). The patient was also known to have recurrent dislocation of the patella. The right radial head was removed, with good results, and correction of the left elbow was planned for a later date. Other pertinent findings were fissuring of all the nails and hypoplasia of the patellae. Iliac horns were not demonstrated. This patient's mother, an aunt and an uncle have involvement of nails, knees and



Figure 2.—(Case 1) Posterior subluxation of radial head.

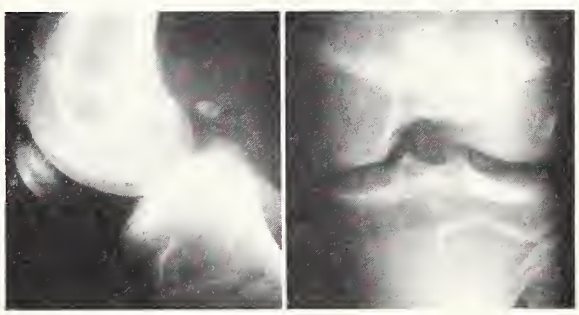


Figure 3.—(Case 1) Hypoplastic patella.

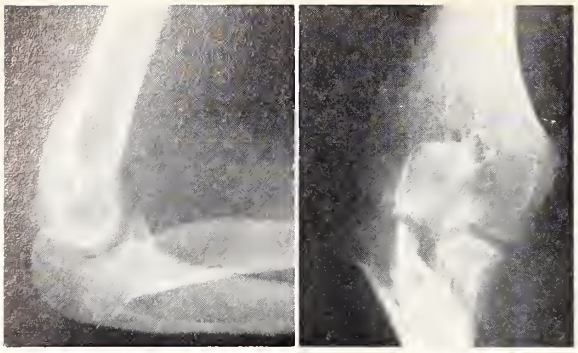


Figure 4.—(Case 2) Dislocation of radial head with greater deformity than in Case 1.

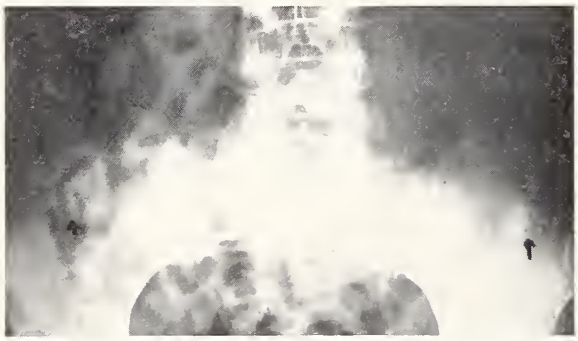


Figure 5.—Rudimentary iliac horns (arrows) in mother of patient in Case 2. (Propositus did not exhibit this manifestation.)

elbows. The mother had iliac horns as well (Figure 5).

Inquiry elicited that the maternal grandfather had involvement of the nails, knees and elbows. He had three sisters and a brother with reportedly no involvement.

Results of routine blood studies and urinalysis of the patient and her mother were within normal limits.

Summary

The principal manifestations of hereditary osteo-onycho-dysplasia consist of nail dystrophy, elbow dysplasia, hypoplasia or complete absence of patella, and the presence of iliac horns. Nephropathic concomitants, present in some cases, may cause death.

In two cases here reported, manifestations of the condition were not present in siblings but were known in some progenitors.

REFERENCES

1. Brixey, A. M., Jr., and Burke, R. M.: Arthro-onychodysplasia. Hereditary syndrome involving deformity of head of radius, absence of patellae, posterior iliac spurs, dystrophy of fingernails, Amer. J. Med., 8:738, June 1950.

2. Carbonara, P., and Alpert, M.: Hereditary-osteo-onychodysplasia (HOOD), Amer. J. Med. Sci., 248:139, Aug. 1964.

3. Cosack, G.: Hereditaire arthro-osteo-onychodysplasie mit beckenhornern (Turner-Keiser-syndrome) in verbindung mit hyposideramie, Ztschr. Kinderh., 75:449, July 1954.

4. Duncan, J. G., Souther, W. A.: Hereditary osteo-onychodysplasia. The nail patella syndrome. J. Bone Joint Surg., 45-B:242, May 1963.

5. Duthie, R. B., and Hecht, F.: The inheritance and development of the nail patella syndrome, J. Bone Joint Surg., 45-B:259, May 1963.

6. Elliott, K. A., Elliott, G. B., and Kindrachuk, W. H.: The "radial subluxation fingernail defect—absent patella" syndrome. Observations on its nature, Amer. J. Roentgen., 87:1067, June 1962.

7. Gibbs, R. C., Berczeller, P. H., and Hyman, A. B.: Nail-patella-elbow syndrome, Arch. Derm., 89:196, Feb. 1964.

8. Hawkins, C. F., and Smith, O. E.: Renal dysplasia in a family with multiple hereditary abnormalities including iliac horns, Lancet, i:803, 29 Apr. 1950.

9. Jameson, R. J., Lawler, S. D., and Renwick, J. H.: Nail-patella syndrome: Clinical and linkage data on family, G. Ann. Hum. Genet., 20:348, May 1956.

10. Lawler, S. D., Renwick, J. H., and Wildervanck, L. S.: Further families showing linkage between the ABO and nail-patella loci, with no evidence of heterogeneity, Ann. Hum. Genet., 21:410, June 1957.

11. Lester, A. M.: Familial dyschnodroplasia associated with anonychia and other deformities, Lancet, ii: 1519, Dec 1936.

12. Levin, B.: Gonadal dysgenesis. Clinical and roentgenologic manifestations, Amer. J. Roentgen., 87:1116, June 1962.

13. Lacroux, R., Philippon, J., and Poirier, J. P.: Hereditary onycho-arthro-osteodysplasia (Touraine's onycharthrosis), Ann. Derm. Symph., 87:382, July-Aug. 1960. (Fr.)

14. Lucas, G. L., and Opitz, J. M.: The nail-patella syndrome, J. Pediat., 68:273, Feb. 1966.

15. Muth, R. G.: The nephropathy of hereditary osteo-onychodysplasia, Ann. Intern. Med., 62:1279, June 1965.

16. Renwick, J. H., and Lawler, S. D.: Genetical linkage between the ABO and nail patella loci, Ann. Hum. Genet., 19:312, June 1955.

Intrauterine Transfusion of Twins

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BEGINNING WITH the first case report of a successful fetal transfusion by Liley,[10] numerous articles have appeared in the literature describing modifications, complications and results with this procedure. The following is a report of fetal trans-

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fusions of twins in a patient with severe Rh sensitization. This case is reported because it demonstrates several problems which were encountered. We believe these problems are not unique, but experience with twin gestation, although reported in the literature, has not been outlined in detail.[5,8,9,11]

Report of a Case

The patient was a 35-year-old, gravida 5, para 4, whose last menstrual period was 1 April 1966, and her expected date of confinement 6 January 1967. Her blood type was A, Rh negative (D), indirect Coombs (D) 1:2048. Her husband was homozygous for D. Between 1952 and 1961 the patient had four term pregnancies, all babies being born without evidence of erythroblastosis. All Rh titres during her previous pregnancies were negative. The patient's indirect Coombs titre was found, in the second trimester of this pregnancy, to be 1:1024 and she was noted to have a twin gestation. At the 32nd week of gestation she was referred to the Colorado General Hospital for evaluation. Specimens from both amniotic fluid sacs analyzed by the chloroform extraction technique[3] revealed that Twin A had an optical density (O.D.) of 0.29, and Twin B an optical density of 0.16 at 450 mu absorption peak, both in Zone III. A fetal transfusion with 75 ml of O negative packed red cells was performed without difficulty on Twin A. Before the infusion of blood, 8 to 10 ml of ascitic fluid were removed from the peritoneal cavity. Both twins did well following the first transfusion. Four days later, a specimen from the amniotic sac of Twin B revealed an O.D. of 0.46 at 450 mu, suggesting a deterioration of the condition of Twin B. Consequently, a fetal transfusion using 80 ml of packed O negative red blood cells was carried out on Twin B on 23 November 1966. Less than 5 ml of ascitic fluid was aspirated before transfusion. Although this transfusion was somewhat more difficult because the first needle introduced was put into the fetal bowel and a second transfusion needle was required to introduce the blood into the peritoneal cavity, both fetuses appeared to tolerate the procedure well.

Twenty-four hours later, fetal heart tones were heard from both fetuses. Approximately 48 hours after the second fetal transfusion, fetal movement could not be felt by the patient and fetal heart tones could not be heard in the area of Twin A but could be heard from Twin B. Ninety-six hours after the second transfusion no fetal heart tones could be heard. Ultrasound and x-ray examinations of the maternal abdomen were equivocal for fetal death. Six days after the second fetal transfusion, spontaneous labor ensued and following an uneventful labor, two macerated stillborn fetuses were delivered without difficulty. Both fetuses were females, and examination of the placenta revealed monochorionic, diamniotic membranes indicating monozygotic twins.

At postmortem examination Twin A weighed 1,970 gm. Subcutaneous tissues were decidedly edematous and the peritoneal cavity contained 50 ml of a serosanguineous fluid (adult hemoglobin). The only abnormality of the internal organs was splenomegaly. Pulmonary capillaries were engorged with nucleated red blood cells. The body of Twin B weighed 2,270 grams and there was severe generalized edema compatible with the diagnosis of hydrops fetalis. The peritoneal cavity contained 70 ml of serosanguineous fluid (adult hemoglobin) and the spleen was enlarged. Numerous nucleated red cells were noted in capillaries throughout the tissues. Examination of the 1,050-gm, edematous placenta showed findings typical of severe erythroblastosis fetalis with pale, thick, edematous cotyledons. Nucleated red blood cells were present in the vessels and there was persistence of the cytotrophoblastic cells.

Discussion

This case presented several distinct clinical problems. In a twin gestation, accurately obtaining samples from the amniotic fluid sac of each fetus is extremely difficult. The injection of methylene blue has been recommended as a means of differentiating the two fluids.[8] However, our experience with four sets of twins has indicated that this is at best a difficult procedure. In the patient presented, ultrasound placentography indicated a left lateral implantation site. Amniocentesis in each of the four quadrants of the uterus was performed, and 450 mu O.D. absorption peak studies on each specimen of fluid showed insignificant variation (0.29 ± 0.04). This suggested that only one amniotic sac had been sampled. Only after amniography was performed was a successful tap into the second amniotic cavity accomplished, revealing a 450 mu O.D. of 0.16. By outlining the extent of the amniotic cavity of Twin A, the amniogram allowed a more accurate placement of the needle through the right flank into the amniotic sac of Twin B.

In a twin gestation in which the mother shows evidence of sensitization to the D antigen, the severity of the disease may be quite different in each twin. This may be true even in monozygotic twins.[4,6] There has been no definite precedent established concerning which twin should be used as a guide to therapy. However, it has been suggested that management be governed by the most severely affected twin.[8] Because fetal transfusion carried a significant risk of fetal death, the outcome for the total pregnancy if one twin should die *in utero* had to be considered. There is evidence that the death of one twin *in utero* does not necessarily jeopardize the other.[7]

It has been established that amniotic fluid analysis is the most reliable method available for determining the severity of erythroblastosis in the fetus. From our experience with single gestations, the initial amniotic fluid values indicated that for Twin A either immediate delivery or intrauterine transfusion was required (450 mu O.D. = 0.29), while Twin B (450 mu O.D. = 0.16) could be managed conservatively by repeating the amniocentesis within seven days.[2] Because the estimated hazards of prematurity and severe erythroblastosis at 32 weeks' gestation were thought to be greater than the risks of fetal transfusion, and on the premise that management should be based on the most severely affected twin, the decision was made to transfuse Twin A. One week after the initial amniocentesis, Twin B was found have an amniotic fluid 450 mu O.D. of 0.46. Because in our laboratory this value falls in the range for fetal transfusion, with the intention to provide maximum maturity for both twins, we decided upon fetal transfusion for Twin B.

It was apparent following the amniogram of Twin A that the position of this twin changed considerably in a few hours. Consequently, we utilized the contrast material in the gastrointestinal tract to definitely identify this twin as the one requiring the first transfusion (Twin A). Purposely, an amniogram was not done on the second twin lest it cause confusion as to the identity of the untransfused twin (Twin B). We were surprised to find that the placement of the transfusion needle into the peritoneal cavity of each twin was not more difficult than has been our general experience with single fetuses of the same size.

Another but largely theoretical consideration was the possible effect of vascular anastomosis in monozygotic twins.[1] There was no way of determining either the zygosity of the twins before delivery, or, if the twins were monozygotic, the presence of vascular communications. However, it is conceivable that vascular anastomosis might be beneficial to the second twin, who thus would share in the absorption of adult red cells. On the other hand, such sharing would dilute the general effect of these cells and diminish their effectiveness for the first twin.

Finally, there was the dilemma which must be faced in many fetal transfusions in which the fetus dies *in utero*. The postmortem examination indicated successful transfusions and evidence of severe erythroblastosis fetalis with the suggestion of hydrops fetalis in each infant. However, the specific cause of death remains unknown, and whether fetal transfusion was the primary cause of death, or was a contributory factor or was completely incidental to the natural course of the disease cannot be ascertained.

Summary

In fetal transfusion of twins in a patient with severe Rh sensitization, some of the difficulties inherent in this procedure were encountered. The value of performing an amniogram in only one twin was emphasized: (1) as an aid to accurate amniotic fluid sampling from each twin and (2) as a method to differentiate one twin from the other during the period of clinical management.

REFERENCES

1. Benirschke, K., and Driscoll, S. G.: The placenta of multiple pregnancy, The Pathology of the Human Placenta, Chapter V, Springer-Verlag, New York, 1967.
2. Bowes, W. A., Jr., Drose, V. E., and Bruns, P. D.: Amniocentesis and intrauterine fetal: Transfusion in erythroblastosis, Amer. J. Obstet. Gynec., 93:822, 1965.
3. Brazie, J. V.: Amniotic fluid pigment identification, Report of 53rd Conference on Pediat. Res., Sept. 1966, pp. 46-48.
4. Cathie, I. A. B.: The treatment of erythroblastosis foetalis, Arch. Dis. Child., 21:229, 1946.
5. Crosby, W. M., and Gheen, D. L., Jr.: Intrauterine transfusion of twins: Report of a case, Obstet. Gynec., 29:674, 1967.
6. Demy, N. G.: Erythroblastosis fetalis in identical twins, Amer. J. Obstect. Gynec., 47:554, 1944.
7. Eastman, N. J., and Hellman, L. M.: Williams Obstetrics, (ed. 13), Meredith Publishing Co., 1966, p. 664.
8. Fricsen, R. F.: Results and complications of intrauterine transfusion before delivery, Report of 53rd Ross Conference on Ped. Res., Sept. 1966, p. 91.
9. Gordon, H., Grausz, J. P., Raphael, M., and McClure-Browne, J. C.: Experiences with intraperitoneal transfusion, J. Obstet. Gynaec. Brit. Comm., 73:917, 1966.
10. Liley, A. W.: Intrauterine transfusion of foetus in haemolytic disease, Brit. Med. J., 2:1107, 1963.
11. Queenan, J. T., and Douglas, R. G.: Intrauterine transfusion: A preliminary report, Obstet. Gynec., 25: 308, 1965.

Quality in Health Care

A Report on the 1968 National Health Council Forum

MORE THAN 800 persons attended the national conference in Los Angeles on March 15 to 17 to participate in discussions which dealt with the various components and elements contributing to the attainment of quality in health care.

The National Health Council, a 75-member organization with wide representation from the public and private sectors of most of the health professionals and voluntary agencies, held its sixteenth health forum on the subject "Quality in Health."

Chairmanship of the meeting was delegated to Samuel R. Sherman, M.D., of San Francisco, a past president of the California Medical Association. Dr. Milford O. Rouse, President of the American Medical Association as well as Dr. Dwight L. Wilbur, AMA President-Elect and Dr. Walter C. Bornemeier, Speaker of the AMA House of Delegates, were in attendance. Other prominent AMA participants were Dr. Charles L. Hudson, Dr. Gerald Dorman, Dr. Burt Davis, Dr. Robert Long, Dr. George Slagle and Dr. Phillip Hampton. CMA was also represented by its then President, Dr. John G. Morrison, President-Elect Malcolm C. Todd, Dr. Jean Crum, Dr. Sanford Feldman, Dr. George Bessom, Dr. Alan Briney and Dr. Malcolm S. M. Watts. More than 200 other practicing physicians from all over the United States were also in attendance for the three-day meeting.

Papers which had been commissioned by the conference planning committee, and which served as the basis for panel and group discussions concerned themselves with manpower utilization, continuing education, accreditation, certification and licensure, consumer utilization, the hospital utilization review mechanism, design of facilities, components and organization of interdisciplinary teamwork, financing and methods of payment and measurement. Other presentations dealt with current legislative proposals now being implemented through such programs as heart, cancer and stroke, comprehensive health planning, rehabilitation and neighborhood health centers.

While no recommendations were, or could be, adopted by the Forum, the conference served as a mechanism to bring together a broad representation from various fields involved in the scientific, medical, research and socio-economic aspects of health care for an exchange and synthesis of ideas and concepts, most of which have appeared in the literature and have been discussed and debated over the years.

The conference can perhaps best be capsulized by the observation that there was widespread recognition that the components of quality encompassed considerably more than just the nature and standards of care provided by the physicians; that every member of the health care team had a role and responsibility as a contributor to quality health care; that equipment, facilities, the financing mechanisms involved, and the behavior and attitudes both of providers and consumers—all represented factors and elements in maintaining and improving levels and quality of health care. In this regard, it is particularly significant to note that the *Third Progress Report* of the CMA Committee on the Role of Medicine in Society had not only anticipated some of the outcomes of various discussions, but that the definitions it arrived at received considerable recognition and agreement.

Although several speakers acknowledged that quality could not be "measured," it was apparent that the quest for establishing improved evaluation and assessment techniques will be an ever-present goal as well as a demand upon the health care professions.

Panel discussions produced evidence of dissatisfaction with licensure mechanisms, suggested the

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need for recertification, called for the coordination of the members of the health care team, urged the incorporation of continuing education in the total educational process, pleaded for a reexamination of the skills, training and education required for various levels of professional activity, suggested different models for the organization and provision of medical care, urged the setting of standards by the various professional groups involved in the rendition of services, recommended the coordination of such standards by representatives of all disciplines involved, and observed that quality was an elastic, never-ending, concept which required constant surveillance and evaluation. One of the main threads which ran through all discussions was the need to involve the client, or consumer, in the decision-making or evaluation processes, in order to promote visibility of action as well as to benefit from the suggestions and experiences patients have.

The meeting was a harmonious one—with virtually all persons recognizing that they were working toward a common goal in which voluntary efforts could best prevent government interference with, or domination of, a crucial aspect of medical care.

The 1969 National Health Forum, to be held in New York City, will have poverty as its theme. Unquestionably, the provision, availability, accessibility, continuity, comprehensiveness and quality of medical care will be parts of the discussion at that time.

SAMUEL R. SHERMAN, M.D.

Efficiency and the Public's Health

CARL E. ANDERSON, M.D., *Santa Rosa*

■ *The Governor's Survey on Efficiency and Cost Control, established by Governor Reagan's executive order, was a non-profit, bipartisan, privately financed management analysis of State administration conducted by private citizens, including physicians, during 1967 for the purpose of achieving improvement in administrative procedures and operating economies in State government.*

State employees and appointed department heads offered many valuable suggestions and cooperated fully with the survey team.

Two hundred recommendations were submitted to the Governor for improvement in the Departments of Public Health and Mental Hygiene, the Office of Health Care Services and the organizations under the Secretary of Human Relations.

The recommendations for the health-related administrative units concerned reorganization and consolidation of departments and units, improvement in administrative and operating methods and improvement of services. Annual savings of several hundred million dollars could result.

None of the recommendations were for reduction in services and none concerned individual employees or appointees.

Assistance in and support for the implementation of the recommendations will be needed from legislators, responsible citizens and organizations interested in efficient and economical government.

EXPENDITURES OF TAX MONEY to improve the health of Californians have risen during the past ten years at eight times the rate of population increase. A similar disproportionate growth has occurred in the number of State employees and in the cost of State government generally. By comparison, the rates of increase in the cost of private health services — from 4 to 7 percent per year — are miniscule.

Recognizing that the pyramiding costs of State government, including public health, could soon bankrupt our economy, Governor Ronald Reagan, in the first month of his administration, called for help from the private sector of business, industry and the professions. In response, and at no expense to the taxpayers of the State, a non-profit organization — the "Governor's Survey on Efficiency and Cost Control"—was formed. With bipartisan support, and financing from private industry, 250 top-level businessmen and four physicians conducted a full-time, on-the-spot, in-depth study of State administration over a period of nearly eight months.

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The physicians were assigned as members of the survey teams investigating the efficiency and the effectiveness of those departments most closely related to health services: Mental Hygiene, the Medi-Cal Administration, Public Health, and the organizational structure under the Secretary of Human Relations.

The survey developed recommendations to bring the most modern business methods into the administration of State government. Programs were not evaluated on their merit, rather on the basis of whether they were being administered efficiently, to provide the people of the State the greatest benefit with the least expenditure of tax money. Employees were not judged individually. Jobs were evaluated as to whether job requirements and productivity measured up to the standards acceptable to private industry.

The State employees, from clerks and truck drivers right up to department heads, were most cooperative. In particular, Doctor James Lowrey, Doctor Lester Breslow, Mr. Carrell Mulder and Mr. Spencer Williams from their top administrative positions, insisted that their subordinates assist the survey teams in every reasonable way. Without this cooperation, our efforts would have been wasted.

By October 1967, the preliminary reports and recommendations had been developed. In the health area alone, the reports, working papers and supporting materials filled several large filing cabinets. In order to reduce this vast amount of material to the size of a workable document, tremendous condensation was required. The result: "Summary Report and Recommendations," containing 149 pages, was published in February of 1968.

More than 2,000 specific recommendations for improvement are summarized in the Report. When these are fully implemented they could result in annual savings of 233 million State tax dollars, 67 million local tax dollars and 97 million dollars from Federal taxes. Additionally, a potential of 250 million dollars can be saved in one-time or capital expenditures.

Some of the recommendations were implemented by department heads even before the survey was completed, others are now being effected. Those not yet put into effect require legislative approval, or in a few instances appear to require actions which are not immediately practical. In no instance have services to the people of the State been reduced or curtailed as a result of the Survey recommendations.

Two hundred of the recommendations pertained directly to the health-related functions of State government. These can be divided into three broad categories:

(1) Reorganization,

(2) Improvement in administrative procedures and methods,

(3) Improving services.

Some examples are cited in the following paragraphs.

Reorganization

This is a major undertaking in any department or in any business. Legislative, as well as administrative, action is necessary. Some health-related units were found to be outmoded in their organizational structures and, therefore, incapable of doing their jobs efficiently.

Some specific examples:

Forty-three bureaus and nearly a hundred individual projects in the Department of Public Health were found to be functioning almost as independent units, with no clearly defined lines of management responsibility. Recommendations for consolidation and realignment would reduce the number of bureaus to 23, directly responsible to five division chiefs who in turn are directly accountable to the Head of the Department.

The Board of Public Health is charged with setting general broad policies for the protection of the public health. As a result of the board's location in the State's administrative organization, it has no influence on such important health matters as mental health, rehabilitation, Medi-Cal, drug abuse or the medical programs in penal institutions. The recommended establishment of a higher level State Health Council, advisory to the Secretary of Human Relations and the Governor would correct this organizational deficiency and promote better coordination of all of the health programs for which the State is responsible. The Board of Public Health, somewhat reduced in size, would continue to assist the Health Director in performing his duties.

The organizational structure for the administration of the Medi-Cal program — responsible for spending nearly one billion dollars per year — was found to be poorly put together and, at the same time, to be only one of some 15 units of State

government doing the job of purchasing health care services.

Recommendations included elevation of the Office of Health Care Services to departmental status, centralization of health care purchasing in the new department and the creation of a top level administrative task force. This latter recommendation has been implemented. Doctor Malcolm Todd, President of the California Medical Association, is a member of this advisory group.

Improving administrative procedures and methods

Health statistics are being collected in well over 100 different bureaus and program units in several departments. Outdated systems such as manual tabulation, sorting and analysis consume countless man-years. Hundreds of thousands of dollars could be saved by modern automatic and electronic data processing.

Much of the data collected is in such form that it cannot be correlated with the statistics produced in other units and thus the potential value of the data for broad-scale epidemiologic study and research is lost.

Recommendations for improvement include centralized control and coordination of all health data systems in a management services unit under the Secretary of Human Relations. Management services units in individual departments would be responsible for control of departmental data handling.

Other recommendations for improving administrative efficiency include:

Application of employee work standards, separation of research from production and service activities, centralization of secretarial and clerical personnel within departments and divisions, avoidance of duplication of functions in inspections, licensing and certification, and application of industrial standards for use of space and equipment.

Improvement of Services

Changes were recommended to improve some health services. Some of the recommendations will require legislative concurrence.

These recommendations include:

Greater emphasis on the responsibilities of local health departments, with the State providing assistance and support where necessary.

Improvement in the food services and dietary management in State mental institutions.

Greater emphasis on health education especially in the fields of drug abuse, accident prevention and mental illness.

An intensified program of preventive dental health activities.

Local control of mental health clinics and the medical and surgical treatment of state mental hospital patients in general hospitals.

Only a few illustrative examples of the Survey's many recommendations have been listed. Persons interested in the full "Summary Report" should contact the office of the Governor's Survey on Efficiency and Cost Control, Post Office Box 931, Sacramento, California 95804.

"Reagan's Raiders," as the survey workers were sometimes called, have a deep feeling of satisfaction in having pointed out ways in which our huge State government may do a better job for the people and still achieve economies. This goal will not be attained unless the far-reaching recommendations are put into effect. Assistance from responsible citizens, interested organizations and our legislators will be necessary. Members of the survey team are available to provide additional information to groups or organizations desirous of achieving efficient, economical State government.

A Role for Medicine in a New Era of Health Care

Part II

Fourth Progress Report of the Committee on the Role of Medicine in Society, California Medical Association

A THESIS WAS developed in Part I of this report which the Committee believes can serve as a basis for action programs for physicians and organized medicine in a new era of health care. A role is proposed which should be inherently natural for physicians, utilizing the professional expertise and experience of the medical profession to strengthen what is weak and to repair what is defective in health care, just as the individual physician seeks to do with his patient. This proposal also recognizes that understanding and cooperation, whether with a patient or with public opinion, are essential if best results are to be achieved.

I. *Disparate Expectations and Resources*

The Committee believes that for the foreseeable future a national commitment in health care which is theoretically almost infinite will be pitted against national resources which are destined always to be limited by comparison, and for practical purposes, quite finite. This disparity is certain to dominate many aspects of health care. Its ramifications are already evident in growing problems with respect to the services, facilities and manpower available for the delivery of health care, and they are becoming increasingly apparent in many aspects of education and research in the health sciences as well. The Committee believes that individual physicians and organized medicine have personal and corporate responsibilities to develop professional expertise and experience in these areas and to apply this expertise and experience effectively to these problems.

It may be expected that the following developments will result from this predictable and continuing tussle between requirements and resources:

- Requirements and needs in every aspect of health care will be more precisely defined and quantified.
- Availability and utilization of resources will be more carefully monitored.
- Economy and efficiency will be more heavily emphasized.
- Quality and effectiveness will be better documented.
- Continuing pressures will be needed to maintain adequate funding from both public and private sources.
- Social, economic and political factors will become more decisive determinants in both public and private sectors and to a substantial extent these will reflect the public attitude or opinion of the moment.

II. *Defining the National Purpose*

The present state of knowledge with respect to the national purpose and its inevitably disparate resources for health care may be compared with that obtaining in any new discipline or body of knowledge in an early stage of development. A new science or body of knowledge usually begins its development by going through a period during which its various elements are defined and classi-

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Committee on Role of Medicine in Society: Gerald Besson, Burt L. Davis, Sanford Feldman, Elmer F. Gooel, Sherman Mellinkoff, Malcolm C. Todd, and Malcolm S. M. Watts, chairman; and ex officio Carl E. Anderson, and Jean F. Crum.

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fied. These working definitions and classifications must initially be culled from whatever theory, knowledge or experience may be at hand. With definitions and classifications established it becomes possible to study characteristics and relationships and to pose questions both of theory and of fact. Greater precision is achieved when quantitative measurements can be applied.

The Committee believes that the national purpose in health care should now be given this kind of scrutiny. It further believes that organized medicine can and should make an important contribution by bringing its knowledge, expertise and experience to bear. The problem may be approached initially by examining a number of the phrases and cliches which appear to have gained public acceptance in their generality, and by seeking to identify and spell out the specifics inherent in these generalities. The statements of Congressional intent, to be found in a number of the laws enacted in recent years, should be an important source of material for study. The following are examples of statements which might be critically scrutinized as to meaning and implications:

- Health care is the right of every individual.
- There should be a personal physician for every person.
- Comprehensive health services are to be equally available to all.
- There should be mainstream medical care for all.
- Health and health care are a public responsibility.
- A pluralistic approach to providing health care involving both public and private sectors is to be tried.
- Local initiative and local control are to be emphasized.
- There is to be no interference with existing patterns of health care.

Recommendation:

The Committee recommends that the California Medical Association or the American Medical Association examine the meaning and implications of the national purpose in health care with the intent of giving more precise definition to the aims which appear to have public acceptance, and to their implications, in order that medicine may clarify its role in this new era of health care.

III. *Defining the Scope and Responsibility of Medicine*

Parallel to the need for more precise definition of the national purpose is a comparable need for a clearer understanding of what should be the scope and responsibility of medicine in this new era of health care. It is surprising but true that this is by no means agreed upon or spelled out. There is a wide spectrum of opinion, both within and outside of the profession.

The scope and responsibility of medicine must relate closely to what is meant by health and health care, and these concepts are currently undergoing reassessment and change. Under the influence of cultural forces and the impact of scientific progress, the concept of health is coming to embrace more than the mere absence of disease or injury. The World Health Organization calls it a "state of complete physical, mental and social well being." In other terms it has been defined as a satisfactory adjustment between a human being and the many aspects of his environment. It has been described from the viewpoint of the patient, the health professional, the social scientist. It has been studied by governmental bureaus and public health officials. The Committee believes that the medical profession should now examine the meaning of health and utilize its expertise and experience to develop guidelines to make the concept more meaningful to the national purpose.

Scientific progress and social change have also given rise to a number of "new dimensions" of modern medicine in modern society. The two-party relationship between doctor and patient has become a multi-party phenomenon. The ramifications of specialization in both medicine and society, rising costs, questions of quality and efficiency, new attitudes of patients and the public toward health and health care, "social disorders" of human behavior in modern society, new and far-reaching demands on medical education, and the new relationships of medicine with the law and with politics are surely "new dimensions" which are pertinent to the scope and responsibility of medicine in this new era of health care.

There is need for closer agreement concerning the scope of the responsibility of the practicing physician. Is this responsibility simply to the patient, to save his life, relieve his suffering or restore his function? Does it also include prevention, rehabilitation or health maintenance? Should it be

concerned with health environment, human behavior as it affects the individual himself and others, or the effectiveness and efficiency of the health care delivery system? Does this responsibility extend even further, to the species? And, if so, are the expertise and experience of the medical profession and the concepts of prevention, health maintenance, diagnosis, treatment and rehabilitation to apply to the ills of a biologic society as well as to the biologic individual?

The medical profession should soon seek a sharper definition of its scope and responsibility, in this new era of health care, first as discussion within its own ranks and then in dialogue with society. Each of the major professions is the most knowledgeable with respect to its own capabilities and limitations, and therefore each logically and traditionally has more or less defined its own area of competence and responsibility. This Committee believes that medicine is clearly the best qualified to define its own scope, and the best qualified to take the necessary steps to carry out its self-determined responsibilities. These actions should be taken promptly and expertly. Failure to do so could quite conceivably result in erosion and possibly destruction of the very capability for self-determination which both the profession and its members now possess, and which is so essential to their effectiveness.

Recommendation:

The Committee recommends that the California Medical Association or the American Medical Association undertake, in collaboration with others, to:

(1) *Examine the impact of scientific advances and cultural influences upon the concepts of health and health care;*

(2) *Consider the many dimensions of modern medicine in modern society which have resulted therefrom;*

(3) *Develop an appropriate definition of health, outline the scope of medicine with respect to this definition and delineate suitable roles and responsibilities of the individual physician and organized medicine in terms of this definition and scope.*

IV. *A Role of Flexible and Informed Advocacy*

The demonstrated effectiveness of organized advocacies in accomplishing their goals in the pluralistic society of this nation has been noted in Part I of this report. It has also been noted that when a substantial disparity between expectations and resources in health care becomes identified as a problem, the action taken generally reflects the application of some combination of scientific, humanitarian and economic value systems. This occurs in both the private and the public sectors, where each value system has its own advocates who may be more or less knowledgeable and organized. It was further noted that health care is best served when values, expectations and resources are maintained in some sort of reasonable balance; and that some kind of responsive, knowledgeable force or influence is needed to accomplish this. It was suggested that the expertise and experience of physicians and organized medicine can and should be developed as this responsive and flexible force or influence. The phrase "flexible and informed advocacy" was used to describe this approach.

Many parallels exist between this suggested role of flexible and informed advocacy and the customary role of the physician in his ordinary practice. Whether it is the patient whose health is not as good as he would like it to be, or a health care system which is not as good as the nation would like it to be, the process for remedying the situation is much the same. A diagnosis must be made, and if the fundamental cause cannot be eliminated and a cure easily effected, then a program of treatment designed to improve the situation is instituted. This program must have the cooperation and support of the "patient" if it is to be successful.

The procedure to be followed is familiar to physicans. The complaints are identified, the characteristics of the presenting problem are studied, the past history, family history and social history are reviewed to discover any important factors which may have led up to the present situation. A careful examination is made and the necessary research or studies are carried out to provide additional needed information. A plan of treatment is then determined. The patient is fully informed of the plan and must be convinced of its importance and value in order to secure his cooperation and support in carrying it out. It is the expertise and experience of the physician which guide this process and which are brought to bear in both diagnosis and treatment. While many other professions may be involved in one or another aspect of the health care of this patient, the central expertise is that of the physician and the central body of knowledge

is that of medicine. Technical skills, humanitarian and economic values, and the opinions and beliefs of the patient are all of essential importance and are all woven into the treatment program which the physician advocates.

The concept of a flexible and informed advocacy for the medical profession suggests that the aim "to promote the art and science of medicine and the betterment of the public health" can best be served in this new era of health care if the expertise and experience of physicians and organized medicine become organized both on an individual and a corporate basis and are then brought to bear in the physician's practice, in his community activities, and in the corporate actions of the organized profession.

The practicing physician can apply this principle in his own practice to assess his own performance in terms of his personal responsibility to develop and use his knowledge and expertise in the most effective and efficient ways he can so that he may make his most responsible individual contribution toward accomplishing the national purpose in health care. More specifically, he can examine his knowledge and performance in terms of scientific competence, humanitarian accomplishment and economic efficiency, and organize his studies and practice so as to strengthen those values in which he finds himself deficient. As a citizen in his community, he can apply his special knowledge and expertise in flexible fashion to guide and support those who are working to strengthen scientific, humanitarian and economic values in health care. As a member of organized medicine he can support his profession in its corporate policy of flexible advocacy for better health care and draw upon its resources of expertise and experience to help him apply its principles in his own practice and in his own community.

A role of flexible and informed advocacy, whether on an individual or a corporate basis, requires accurate facts and dependable information which are readily at hand, and easily available means to exert constructive ideological, social, economic and political influence. These are the essential requirements for influencing the course of events in the action process of this free pluralistic society.

Recommendation:

The Committee recommends that the California Medical Association and the American Medical Association explore the concept of "flexible and informed advocacy" and its possible uses as a means to "promote the art and science of medicine and the betterment of the public health."

V. *A Body of Knowledge and Expertise in Health Care*

Just as a physician who is unaware of present-day knowledge in medical science is a poor physician and not likely to be very effective in his practice, so a profession which lacks a body of authoritative knowledge and dependable data in the field of health care is unlikely to have very much success in influencing the course of events. The record shows that organized medicine has been at its most effective when it has been in possession of such authoritative facts and at a distinct disadvantage in their absence.

It therefore seems obvious that if the suggested concept of flexible and informed advocacy is to be applied to problems in health care, the expertise and experience of the medical profession and others must be collected, collated, codified and made available for ready use. But this alone is not enough. Definition and measurement are also among the hallmarks of any science, and this is true for the science and technology of health care. It has been aptly noted that whoever establishes the definitions and carries out the most meaningful and accurate measurements will become knowledgeable and authoritative and, by virtue of this authoritative knowledge, most influential in the health care field.

It now seems particularly important that workable definitions and measurements become available for determining the dimensions of the national purpose, the disparity between expectations and resources, the quality and delivery of health care, and the even less tangible aspects of the applicable value systems and public opinion itself.

Dimensions

The Committee believes that the medical profession should contribute promptly, constructively and authoritatively to delineating the national purpose in health care, the meaning of health in today's society and the responsibility of medicine in terms of the national purpose and the definition of health as suggested above.

Disparity

The Committee believes the profession should

address itself more aggressively to some definition and assessment of the disparities between expectations and resources in health care with respect to the many aspects of service, education and research. The many facets of each of these can be considered in terms of manpower, facilities and funding. Measurements or assessments can be made of such things as competence, availability, motivation, effectiveness, efficiency and satisfaction. Much is already being done in many of these areas under a number of auspices, but the information is uncollected and there are many gaps. CMA is particularly in the forefront among medical associations. But there is much more to do, and to date no group or profession has achieved acknowledged competence or leadership.

Quality

The Committee believes that continuing disparity between expectations and resources in health care will inevitably draw attention to standards of quality, or to the lack of them. There will be discussions with respect to what level of quality—whether in health care services, research, education, manpower or facilities—will be paid for with how much money or with how much of the national resources. Such discussions are already occurring, and pressures to develop acceptable standards for quality in many aspects of health care services are rapidly increasing.

Scientific, humanitarian and economic values are all involved. The Committee believes that this important responsibility should be assumed by the private sector and within the voluntary system. There is ample precedent in standards of quality for educational programs and for hospitals and certain other facilities. In a previous report, the Committee recommended that CMA develop a "Quality Assessment Index for Health Care" to help fill this need and to place CMA in an authoritative position with respect to assessment of quality in health services. The Committee still believes that this should be accomplished by CMA, by AMA or by some other segment of organized medicine.

Delivery

There is a growing interest in the delivery of health services. Medical science in this nation is more highly developed than anywhere else in the world, and yet morbidity and mortality data for the United States leave something to be desired. This suggests that present knowledge could be better utilized in health care. There is also the hope that improved services can somehow be rendered more efficiently and at less cost.

The delivery of health services is currently the subject of much discussion, and many studies are being carried out under various auspices. There is much talk of systems and various methods for health care delivery. The Committee reiterates its previously expressed concern that whatever system or method is used will be adaptable to the needs of individual patients rather than the reverse, which would confine the patient and his physician to the requirements of any rigid system and to whatever services happen to be provided within it.

The Committee recognizes that the CMA is now engaged in many sophisticated activities and studies in the field of delivery of health care services. Indeed, it is well in the forefront among state medical associations. However, much more is needed in the way of research and experiment if recognized competence and leadership are to be achieved in this field.

Values and Public Opinion

Since the most satisfactory answers to the various problems of continuing disparity are likely to be found through an interaction of scientific, humanitarian and economic values with public opinion, the Committee believes that substantive studies should be made of each of these important factors. Studies of scientific values should include consideration of the extent to which given knowledge is truly established and accepted, as well as the extent to which it should be applied, and of competence, effectiveness and efficiency in its use. Substantive studies are also needed in sociology, economics and political science as they pertain to health services, education and research. The opinions, beliefs and attitudes of physicians, patients and the public need careful study with respect to what they are, how they are formed, what changes them, how they interact with one another, and how they may be expected to change in the near and more distant future.

Recommendation:

The Committee recommends that the California Medical Association and the American Medical Association expedite and extend their present ef-

forts, and cooperate with others of like purpose, to develop an accurate and dependable body of knowledge to cover every aspect of health care so that the authoritative expertise and experience of the medical profession may be made readily available to physicians and to any others who seek "to promote the art and science of medicine and the betterment of the public health."

VI. *Aims and Strategy*

The aim of the physician is to try to strengthen what is weak and to repair what is defective in health and health care. His plan for a remedy is called treatment when directed toward patients, but may appropriately be called strategy when it refers to the more general aspects of health care.

The disparity between expectations and resources inevitably gives rise to complaints which may come from patients, physicians, "third parties," government, the public or elsewhere. Just as in medical practice, complaints usually reflect problems and a need or desire to improve the situation; and in such circumstances advocates with well-meaning but perhaps poorly informed advice are apt to appear upon the scene and proffer their advice with any means at their disposal. At this point, just as in medical practice, the medical profession may appropriately enter into the situation, hear the complaints, study the facts bearing upon the problem, bring to bear its body of knowledge and expertise in health care, and plan a positive program of remedy. It then may undertake whatever action or advocacy is necessary to bring scientific, humanitarian and economic values appropriately into play and to persuade or influence the physician, the patient, the community, the public, the legislature, or whoever, to take the needed remedial action. The Committee believes that the medical profession should always press for realistic goals on one hand, and for adequate resources on the other. In this way, its expert knowledge of the problems and of the values involved can be brought to bear effectively to influence the course of events by means of flexible and informed advocacy.

The aims and strategy referred to in this section may be developed and applied by a physician to his own practice, by a physician or a medical society to health care problems in a community, or by the organized profession on a county, state or national level.

Recommendation:

The Committee recommends that practicing physicians, the California Medical Association, and the American Medical Association examine individual, community, state and national problems in health care as they would any other problem in diagnosis and treatment, by assessing the complaint, studying all the pertinent data and information, and then applying the experience and expertise of the profession to develop a plan for remedy which will take into proper account scientific, humanitarian and economic values, as well as the views and opinions of the public or the patient.

VII. *Effective Organization and Action for Effective Advocacy*

It is not enough simply to define the national purpose, assess the disparity between aspirations and resources in health care, agree upon the scope of medicine's responsibility in present-day society, and develop a readily available body of knowledge and expertise in various aspects of health and health care. Nor is it enough to identify appropriate aims and strategy with respect to any given problem in health care. In this pluralistic society, there must also be an effective advocacy to accomplish what needs to be done, and this requires effective organization of the advocacy and the exercise of an appropriate combination of ideologic, social, economic and political influences, or even pressures. The Committee believes that if medicine is to fulfill its responsibility to improve patient care and to promote "the art and science of medicine and the betterment of the public health" in modern society, there must be further and more detailed study of the actual techniques involved in this essential action process.

Organizing Advocacies

There is a need to develop a skill, even a science, of organizing advocacies which will not only make maximum use of the expertise and experience of the medical profession, but which will also bring into play the strengths and skills of others of like purpose. In organizing advocacies, the attitude of the profession has generally been taken into account, but there has often been less consideration of the opinions of patients, other interested groups, or of the public. As a result, there have been occasions when medicine's advocacy has been less effective than might otherwise have been the case,

and experience has already shown that public opinion can play a decisive role. The Committee believes that the technology of organizing advocacies in present-day American society should be promptly studied.

Ideologic Influence and Action

Elsewhere the Committee has taken note of the physician's concern with the human individual, the biological uniqueness of this individual, and the significance of this in a society composed of such biologically unique individuals who must nevertheless live in close interaction with one another in ever more organized social systems and institutions. It has been suggested that a collective ideology has been gaining ground in this nation, while social recognition of the uniqueness and individuality of each human being has yet to come into its own. It is difficult to "organize" uniqueness, individuality and needs for personal self-fulfillment, and so far there is no strong national "collective" group to give effective expression to the "uncollectible" interests in personal freedom and self-expression which are shared by all individuals. It has been suggested that for many reasons organized medicine might be admirably suited to serve in this role.

The Committee believes that concern with the human individual and commitment to progress and competence in human biology make up a valid ideology for the medical profession which can be developed and employed in many ways to produce a positive influence for better health care, and that the content and potential impact of such an ideology upon medicine and society should be studied further.

Sociologic Influences and Action

Social science pertains to the origin, history and nature of human society. Its subject matter deals with such things as roles, status, symbols, images and organization in and of groups of human beings and society itself. Interactions among individuals and various social groups are facilitated by communications which in turn can influence attitudes with respect to roles, status, symbols, images, and organization. In this very real sense, therefore, sociologic pressures can be exerted through such instrumentalities as "communications," "public information" and "public relations." The Committee calls attention to the fact that *communications* implies an almost mechanical process, *public information* a little more structured dissemination of selected subject matter, and *public relations* a more positive effort to establish rapport and understanding. Medical organizations tend to emphasize one or another of these approaches, none of which fully takes advantage of the possibilities of exercising sociologic influence through communications with individuals and groups, whether within the profession or in society. The Committee believes that the means by which sociologic action may be taken in this new era of health care need further study.

Economic Influence and Action

The medical profession can exercise influence and even pressures to bring about the more efficient and economic use of manpower, facilities, services and funds, whether in the areas of patient care, education or research, but must be in a position to pass on quality if it is to do this authoritatively. The subject matter involves such things as the organization and coordination of health care services, delivery systems, professional manpower alternatives, methods of financing and the regionalization of certain services. Many studies are under way under various auspices, but individual physicians and organized medicine can exert significant economic influence to encourage improved economic efficiency in many aspects of health care where this can be done without sacrifice of quality. The CMA has been a leader among medical organizations in this area of influence and activity.

Looking ahead, it is only realistic to anticipate that in a situation of continuing disparity between great expectations and comparatively limited resources there may be occasions when it will be necessary for organized medicine to bring more direct economic pressure to bear to effect an increased allocation of resources to health care in order to maintain its quality. To date, the use of reason and logic, with the support of public opinion, has sufficed. But there is experience to suggest that this may not always be the case. There are precedents in this nation and elsewhere where stronger measures have been needed. The Committee believes that these should be examined in terms of their capabilities and limitations. They include, for example, the always limited and therefore seldom definitive "strikes" used by physicians in Canada and in many countries abroad, the more selective yet highly effective nurses' strikes which have been carried out in certain areas of this na-

tion, and the more imaginative "heal-in" conducted by the intern and resident staff at an eastern hospital. No physician likes the thought of ever employing tactics which are in any way obstructive to health care, but the thought of any system that would accept or tolerate inadequacies and poor quality in health care is even worse. The Committee suggests that the very existence of such studies on the part of organized medicine might prove to be a strong deterrent to the need for their use.

Political Action Through Involvement

In the long run, the effectiveness of political action is a function of the amount of support behind the action. The medical profession, representing only one in a thousand of the population, and often divided within itself, is seldom if ever in a position to achieve its purposes through the sheer power of numbers. Its political aims must therefore be accomplished by enlisting the support of others of like purpose. The support of policy makers, opinion leaders, legislators and, perhaps most important of all, the support of the public itself, must be won by persuasive, logical and effective presentation of whatever case is to be made. The Committee believes that action through involvement is the method by which this is best accomplished, and this means involvement with other groups and organizations in the private sector, with the policy and decision-making processes in the public sector, involvement in the political process of electing qualified candidates to office and, perhaps most important, involvement in the formation of public opinion. In the political arena the strongest assets of medicine are its well documented knowledge and expertise and good use of this knowledge and expertise in the patient and public interest. The Committee believes that the CMA has shown outstanding leadership in this kind of political involvement, but that its effectiveness might improve further with more study of its methods.

Recommendation:

The Committee recommends that the California Medical Association and the American Medical Association consider the elements of effective advocacy and study what is involved in the organization of such an action program and how better to employ ideologic, social, economic and political influence and action in this kind of positive program.

VIII. *Conclusion*

The responsibility to improve patient care and health care programs which is inherent in the CMA and AMA purpose "to promote the art and science of medicine and the betterment of the public health" calls for informed and positive action by individual physicians and by the corporate profession. It is no longer enough simply to play a passive role and oppose what is thought to be bad. The thesis of this report is that the public policy of the medical profession should be expressed through what was termed a flexible and informed advocacy. The Committee believes that this will prove to be a natural and constructive approach for individual physicians and for organized medicine which can become a powerful and effective force for better health and better health care in this nation.

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California Medicine

EDITORIAL

Biochemistry and Mental States

WITH THE INFORMED JUDGMENT that has characterized his work, Dr. Seymour Kety calls attention to one of the great frontiers of biomedical science in this issue. For the first time in history, science is beginning to make inroads on the biochemistry of behavior. Biochemical process relevant to consciousness, memory, thinking and emotional experience are now being identified. This is, for the most part, very recent work. Even today, the number of excellent scientists working in these areas is small but rapidly increasing. The potential importance of their work is very great.

In any young field, and especially one that touches human experience so intimately, the ratio of hypotheses to verified principles is bound to be high. In his judicious way, Dr. Kety helps us to sort these out. Some of the newer findings are remarkable. For instance, the old notion of the sleeping brain as inactive tissue must now give way. The sleeping brain has, in fact, greatly increased blood flow, sharply elevated temperature, and increased oxygen utilization during periods of rapid-eye-movement sleep. These are the same periods which are characterized by electrical activity of the cortex of an "activated" type, and which are specifically associated with dreaming.

In research on memory, claims have tended to outrun substantial findings; but recent work does point to the importance of protein synthesis in the brain for the long-term consolidation of memory —though not for the immediate acquisition of new information. A rather massive inhibition of protein synthesis is required to demonstrate these effects. It is remarkable that even in the face of such inhibition, new learning proceeds adequately —only retention is blocked. Thus, the biological basis of the distinction between short-term and long-term memory storage is beginning to emerge.

The severe thought disorder of schizophrenic behavior is a crucial area for scientific investigation. This is, after all, a common and severe disorder. Dr. Kety and his collaborators have served as a conscience for investigators of this problem. While most of the early hypotheses have proved inadequate, it is extremely interesting to note that they have served to stimulate basic research of great importance and general applicability—the elucidation of biogenic amine metabolism in the brain and other tissues. The role of disordered amine metabolism in schizophrenia is still far from clear, although worthwhile leads are currently being pursued. However, a genuinely "hot" area of investigation has emerged quite recently, centering on the role of biogenic amines in the regulation of mood and in the depressive disorders. These disorders certainly constitute an important problem in medical practice, not only in psychiatry but in a variety of fields.

Various lines of inquiry are converging to implicate the metabolism brain amines, especially norepinephrine, in experiences of depression and elation. Before long, we may well have a biochemistry of hope and despair. The implications of such research for relief of human suffering need hardly be emphasized.

Physician Manpower

THE IMPENDING NEEDS for physician manpower are truly awesome. The reasons are all too simple and all too obvious. These growing needs are a reflection of an almost exponential growth in medical science and a national and world-wide social commitment to better health for all. Scientific progress may perforce be slowed but it will not stop; while the national and international needs are certain to grow as medical skills improve and as backward peoples and those who are at a disadvantage everywhere demand equal opportunity for health in an increasingly complex and interdependent world society.

Elsewhere in this issue is to be found a joint statement by representativcs of the American Medical Association and the Association of American Medical Colleges calling for immediate substantial increases in the enrollment of existing medical schools and for the prompt creation of new ones to meet longer range needs. The statement also calls for innovation and change in educational programs and for adequate financial support from governmental and private sources.

It is quite obvious that if medicine is to play its proper role in a national and international society and if sick, injured or emotionally disturbed patients are still to be served by physicians and not by machines and technicians alone, then both greater numbers and many new kinds of physicians must be produced as rapidly and efficiently as possible without sacrifice of quality either in the caliber of the student or of his training.

The AMA and the AAMC are to be commended for sounding this call. It is being heeded in California.

The Confusion of Tongues

IN GENESIS IS RECOUNTED the story of the first confusion of tongues. Men had sought to create a direct conduit into Heaven in the form of a huge tower at Babel. The project was foiled when language became confounded and men no longer understood one another's speech. Perhaps there is a lesson in this biblical tale as we ourselves seek to build a conduit to the state of good health in the form of a health care delivery system or systems which will provide equal access to every person as a matter of his right.

There is today a considerable confusion of tongues with respect to what is meant by many of the words and phrases which are commonly used in connection with the provision of health services. To wit:

- The word *consumer* as used in discussions of health care may refer to the patient from the standpoint of a physician, the purchaser of health services in the mind of an economist, and the public itself or the voter in the view of government or a politician.
- *Group practice* may refer to three or more physicians in a single specialty and essentially in solo practice who share certain arrangements for reasons of convenience and economy, it may refer to multispccialty groups or clinics of various size and composition which provide care on a fee for service basis, or it may refer to a multispecialty group which contracts to provide specified groups of persons with all the health services they need for a capitation fee of so much for each person.
- *Closed* panel is a term often applied to the capitation form of group practice but is equally applicable to the larger multispecialty groups whose physician panels are closed and who practice for fee for service. In the more common usage, closed panel refers to situations where a closed group of patients and a closed group of physicians are in an exclusive contractual relationship for health care for a given period.
- The word *Prepayment* may properly be applied to insurance premiums for indemnity or service plans, but there are some who use this term only to mean prepayment by capitation for complete services. These persons usually do not recognize other forms or degrees of prepayment. The recent proposal of the California Medical Association and California Blue Shield to contract with the state to provide all physicians' services for persons under the Medi-Cal program is still another dimension of prepayment.
- *Comprehensive, continuing* and *mainstream*, as used to describe health care and health services, are terms in common use but without generally understood or accepted definition or meaning.

These are only a few examples of the confusion of tongues in health care. It is curious but true that the scientific and technologic aspects have far more precise terminology than do the social, economic

or political aspects of health care. Scientists and technologists have long recognized that they can communicate with one another and make progress only when the terms and symbols they use are clearly defined and the meaning clearly understood by all concerned. Symbolism and communication in the social, economic and political aspects of health care delivery systems or conduit have yet to become scientific in this very basic sense of precise definition of meaning.

The biblical tale told in the eleventh chapter of Genesis and the practical experience of modern science both seem to point to the same thing. We must first unconfound our language so that we can comprehend one another's speech. Only then can we understand one another and by working together make orderly progress toward the heavenly state of good health for all.

Abdominal Aortic Aneurysms

THE PAPER BY Moore and co-authors concerning misdiagnosis in patients with abdominal aortic aneurysms is particularly pertinent when reviewed in the context of the past 15 years of advance in vascular surgery. An untreated abdominal aneurysm is a lesion of a highly lethal potential. The mortality from elective aneurysmectomy by experienced vascular surgeons has shown a progressive decline from the original figures of 20 percent to the present norm of 2 to 4 percent. Yet during this same interval these surgeons have been unable to reduce the mortality for emergency aneurysmectomy for aortic rupture to below approximately 50 percent.

The need for diagnosis before rupture occurs is clear. Reliance upon the former textbook criteria where the diagnosis of aneurysm is suspected only if there exists a large pulsatile mass with pain radiating to the back will allow most aneurysms to go to rupture undiagnosed. In this reviewer's experience with a large series of cases of ruptured aneurysms dealt with on an active vascular surgery service, in over 75 percent of the patients the diagnosis of aneurysm was not made before rupture. Most were free of symptoms until rupture occurred. Ninety percent of these patients had been examined by a licensed physician within the previous year.

The reason for the failure in early diagnosis became clear on review of the preoperative clinical events in the group of patients admitted for elective aneurysmectomy before rupture had occurred. In all of them the diagnosis had been first made by the referring physician. Forty percent of these patients, however, denied any form of abdominal symptoms other than a subjective throbbing sensation in the abdomen in those with particularly large aneurysms. Thirty percent had additional vague abdominal symptoms which prompted diagnostic investigation and from x-ray studies directed toward other organ systems the aneurysm became evident. In most of these patients, however, the size of the aorta could be accurately determined by careful abdominal palpation. That many of the lesions were first found by the radiologist suggests that thorough vascular examination is still omitted by some physicians.

The large number of patients in Dr. Moore's series in whom the diagnosis was missed by both the referring physician and the admitting physician in his own institution indicates that palpation for the size of the aorta was not included in the physical examination. Aortic rupture rarely occurs in aneurysms of less than 8 cm in diameter, yet the admitting physician failed to diagnose aortic rupture in four patients, and even the ward physician erred in three of these patients. Dr. Moore's message is clear and should be read by all members of the medical profession at large.

Information

MEDICAL EDUCATION

A joint statement by the American Medical Association and the Association of American Medical Colleges — March 5, 1968

TO MEET NATIONAL expectations for health services the enrollment of our nation's medical schools must be substantially increased. At a joint meeting held in Chicago on 28 February 1968, representatives of the Board of Trustees of the American Medical Association and the Executive Council of the Association of American Medical Colleges emphasized the urgent and critical need for more physicians if national expectations for health services are to be realized.

National policy which would best meet this need, and would be consistent with the American ideal of equal educational opportunity for all, would provide such educational resources that every young person interested in and qualified for entry to the study of medicine would have this opportunity. Both associations endorsed the position that all medical schools should now accept as a goal the expansion of their collective enrollments to a level that permits all qualified applicants to be admitted. As a nation we should address the task of realizing this policy goal with a sense of great urgency.

In their endorsement of and call for broadening educational opportunity for the study of medicine, both associations stressed that the length of time necessary to realize such a goal does not minimize the need to respond to today's critical shortage of physician manpower. In order to enable the nation's medical schools both to meet today's crisis and to attain the longer-range goal of unrestricted educational opportunity, those responsible for allocation of resources must recognize the magnitude of these tasks.

There are both immediate and long-range steps which should be taken. The immediate steps are:

1. To increase the enrollment of existing medical schools. (Considering the time required to create new schools and to provide a student with a medical education, there is no alternative to this step in meeting our present emergency.)
2. To foster curricular innovations and other changes in the educational programs which could shorten the time required for a medical education and minimize the costs. (In view of the increasing quality of pre-professional education and the growing competence of entering medical students it should be possible to reduce the length of medical education without sacrificing quality. Also, as the amount of clinical experience provided medical students increases, the duration of internship and residency training should be reassessed. The process of educating a physician embraces the entire curriculum from high school through residency training.)
3. To meet the need for innovation in educational programs and to encourage diversity in the character and objectives of medical schools. The development of schools of quality where a primary mission is the preparation of able physicians for clinical practice as economically and rapidly as possible is to be encouraged. (Such schools may have less emphasis upon fundamental biologic research than is appropriate for a number of other schools.)

A longer-range approach to the need for physicians is the development of new medical schools. This approach will not solve our immediate, urgent need for more physicians but it is essential for meeting the national needs of 1980 and beyond. The contribution of such schools to the total capacity of the medical education system is important. The advantages of the organization of as many such centers of medical education and development through the country as consistent with strong programs should be kept in mind.

To supplement the measures enumerated above will require adequate financial support from governmental and various private sources for:

1. Construction of facilities to expand enrollment of existing schools and to create new schools.
2. Support of the operational costs of medical schools.
3. Stimulation and incentive for educational innovation and improvement.

To implement these measures will further require that each medical school and its university reexamine its objectives, its educational program, and its resources to determine how it can contribute most effectively to the national need for more physicians and what financial help it will need to make this contribution. Also required is understanding by the public, the private foundations, industry, local and state governments, and the national Congress—groups which must provide the financial support which is necessary.

Initiative for development of new schools and expansion of the established institutions should be locally determined. Only the governing bodies of schools with ongoing programs in medical education can decide to expand such programs. Institutions wishing to organize new medical schools must assume the responsibility for marshalling the necessary support. Both associations are prepared to lend any assistance they can to such efforts.

In Memoriam

BENNETT, MILTON G. E., El Monte. Died 9 December 1967 in El Monte of arteriosclerotic cardiovascular disease. Graduate of Lincoln Medical College, Eclectic, Lincoln, Nebraska, 1909. Licensed in California in 1917. Doctor Bennett was a member of the Los Angeles County Medical Association.

✣

BURDEN, HAROLD GRAINGER, Napa. Died 6 April 1968, aged 69. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Doctor Burden was a retired member of the Napa County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

CANNON, ABERNATHY BENSON II, San Francisco. Died 10 February 1968 in San Francisco, aged 34. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1960. Licensed in California in 1965. Doctor Cannon was a member of the San Francisco Medical Society.

✣

CHAPPELL, ARVIL ELSWORTH, Vallejo. Died 10 March in Mexico City, Mexico, of heart disease, aged 64. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1929. Licensed in California in 1929. Doctor Chappell was a member of the Solano County Medical Society.

✣

CLARKE, FRED B., Long Beach. Died 23 February 1968 in Long Beach of myocardial infarction, aged 87. Graduate of University of Illinois College of Medicine, Chicago, 1907. Licensed in California in 1922. Doctor Clarke was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

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CLARKE, WILLIAM A., El Centro. Died 17 December 1967 in El Centro of adenocarcinoma of the colon, aged 63. Graduate of University of Illinois College of Medicine, Chicago, 1935. Licensed in California in 1935. Doctor Clarke was a member of the Imperial County Medical Society.

✣

COURVILLE, CYRIL B., Los Angeles. Died 22 March 1968 in Glendale of pulmonary edema due to arteriosclerotic heart disease, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Doctor Courville was an associate member of the Los Angeles County Medical Association.

✣

CURRIER, ALBERT EUGENE, Richmond. Died 28 March 1968 in San Diego of hypernephroma, aged 41. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1952. Licensed in California in 1952. Doctor Currier was a member of the Alameda-Contra Costa Medical Association.

✣

DAVIS, KENNETH SAMUEL, Van Nuys. Died 14 March 1968 in Van Nuys of acute pulmonary edema, aged 73. Graduate of University of Nebraska College of Medicine, Omaha, 1918. Licensed in California in 1924. Doctor Davis was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

DESIMONE, LEON OLIVER, Alhambra. Died 10 March 1968 in Los Angeles of heart disease, aged 63. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Doctor Desimone was an associate member of the Los Angeles County Medical Association.

✣

DIAMONDSTEIN, JOSEPH, Whittier. Died 21 December 1967 in Montebello of carcinoma of the stomach and liver, aged 80. Graduate of Chicago College of Medicine and Surgery, Illinois, 1917. Licensed in California in 1951. Doctor Diamondstein was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

DODGE, WALLACE, Los Angeles. Died 8 March 1968 in Los Angeles of heart disease, aged 74. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1915. Licensed in California in 1915. Doctor Dodge was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

DOTY, EARL WESLEY, Long Beach. Died 25 February 1968 in Long Beach of myocardial infarction, aged 56. Graduate of University of Cincinnati College of Medicine, Ohio, 1943. Licensed in California in 1949. Doctor Doty was a member of the Los Angeles County Medical Association.

GUMMIG, EDWARD A., Pasadena. Died 12 March 1968 in Pasadena of arteriosclerotic cardiovascular disease, aged 84. Graduate of Ensworth Medical College, St. Joseph, Missouri, 1914. Licensed in California in 1920. Doctor Gummig was a member of the Los Angeles County Medical Association.

✣

GUNDRUM, LAWRENCE KRAMER, Los Angeles. Died 18 March 1968 in Los Angeles of carcinoma of tongue with metastases, aged 74. Graduate of Washington University School of Medicine, St. Louis, Missouri, 1919. Licensed in California in 1923. Doctor Gundrum was a member of the Los Angeles County Medical Association.

✣

HARDENBERGH, HELEN, San Jose. Died 12 March 1968 in San Jose, aged 60. Graduate of Rush Medical College, Chicago, Illinois, 1939. Licensed in California in 1942. Doctor Hardenbergh was a member of the Santa Clara County Medical Society.

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KAMMERER, BURLEIGH, Berkeley. Died 8 March 1968, aged 50. Graduate of St. Louis University School of Medicine, Missouri, 1951. Licensed in California in 1952. Doctor Kammerer was a member of the Alameda-Contra Costa Medical Association.

✣

KOSKY, ADOLPH WAINO, Santa Monica. Died 28 March 1968 in Brentwood Heights of coronary thrombosis, aged 69. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1923. Licensed in California in 1923. Doctor Kosky was a member of the Los Angeles County Medical Association.

✣

MACDONALD, IAN GIBBS, Los Angeles. Died 9 March 1968 in San Clemente, aged 64. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1928. Licensed in California in 1932. Doctor Macdonald was a member of the Los Angeles County Medical Association.

✣

MCNERNEY, H. W., Richmond. Died 7 March 1968 in Richmond of generalized carcinomatosis due to papillary adenocarcinoma of thyroid, aged 57. Graduate of University of Nebraska College of Medicine, Omaha, 1934. Licensed in California in 1938. Doctor McNerney was a member of the Alameda-Contra Costa Medical Association.

✣

MUDD, SEELEY GREENLEAF, San Marino. Died 10 March 1968 in San Marino of cardiac myopathy, aged 72. Graduate of Harvard Medical School, Boston, Massachusetts, 1924. Licensed in California in 1928. Doctor Mudd was a member of the Los Angeles County Medical Association.

✣

NG, ELMER, Redwood City. Died 16 March 1968, aged 43. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1946. Licensed in California in 1946. Doctor Ng was a member of the San Mateo County Medical Society.

✣

PAGE, WILLIAM ANTHONY, Antioch. Died 22 March 1968 in Walnut Creek of coronary occlusion due to coronary atherosclerosis, aged 64. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1931. Licensed in California in 1948. Doctor Page was a member of the Alameda-Contra Costa Medical Association.

✣

ROBINSON, JOSEPH, Anaheim. Died 17 March 1968, aged 92. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1898. Licensed in California in 1920. Doctor Robinson was a member of the Orange County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

✣

SHELDON, ROY F., Banning. Died 29 June 1967 in Stanton of injuries sustained in an automobile accident, aged 82. Graduate of University of Colorado School of Medicine, Denver, 1912. Licensed in California in 1919. Doctor Sheldon was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

STEINBERGH, SAUL SORBON, Concord. Died 23 March 1968 in Sarasota Springs, Florida, aged 57. Graduate of Temple University School of Medicine, Philadelphia, Pennsylania, 1935. Licensed in California in 1943. Doctor Steinbergh was a member of the Alameda-Contra Costa Medical Association.

✣

VON GEHREN, EDMUND P. M., San Francisco. Died 16 March 1968 in San Francisco, aged 76. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1936. Licensed in California in 1936. M.D. degree from California College of Medicine, 1962. Doctor von Gehren was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

PUBLIC HEALTH REPORT

Hamlet C. Pulley, M.D., M.P.H.
Acting Director, State Department of Public Health

Abortions— First Annual Report

On 30 January 1968, the California State Department of Public Health, as requested by the Legislature, presented its first annual report on abortions and on the implementation of the new Therapeutic Abortion Act which became effective 8 November 1967.

Spontaneous abortion is a relatively frequent event, with one-fourth of all recognized pregnancies terminating before the 28th week. Information regarding illegal abortion is difficult to obtain because of penal and emotional implications; it must be obtained through interviews with women who may be reluctant to disclose such information or who may not be representative of the general population. In spite of these limitations, illegal abortions in California have been estimated to range from 20,000 to 120,000 per year.

The incidence of therapeutic abortion in various countries varies widely because of differences in legal grounds for abortion and the availability and practice of contraception and sterilization.

In some countries which allow abortion on demand, they at times outnumber births. In the Scandinavian countries in 1965, there were between 50 and 60 abortions per 1,000 births.

In this country available therapeutic abortion data are primarily for individual hospitals, whose corresponding ratios would vary widely depending on the type of population served. However, a recent study of 60 American hospitals showed an overall ratio of two abortions per 1,000 births.

Mortality associated with therapeutic abortion is low compared with maternal deaths from all causes, particularly when abortions are limited to the very early months of pregnancy.

Since the enactment of the Therapeutic Abortion Act, the California Medical Association, the California Hospital Association and the State Department of Public Health and representatives of other medical and special groups have undertaken to inform hospitals of their responsibilities under the new law.

The 453 accredited hospitals in California have been requested to provide the State Department of Public Health information about abortions performed under the provisions of the new Act.

At the time the first annual report to the Legislature was in preparation, statistical information for the first two months (November 8 through December 31, 1967) had been received from about half of the 453 hospitals. Reporting from all hospitals in the state has now been completed.

Of the 453 hospitals reporting, 129 hospitals had received a total of 549 applications for abortion; 438 for mental health, 41 for physical health and 70 for rape or incest. Of the 549 applications received, 479 were approved and 439 performed. (The 40 not performed included those scheduled after the report period.) The 439 women who had abortions ranged in age from 12 to 45; 209 had had at least one previous pregnancy; and all but nine were California residents.

Because of the time factor, it is possible to present only a partial picture of abortions performed under the new law in this first report. Next year's annual report (1969) will be the first in which complete statistical data will be available.

The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers.
A list of new books received is carried on page 63 of the Advertising Section.

PROGRESS IN CLINICAL CANCER—Volume III—Edited by Irving M. Ariel, M.D., F.A.C.S., Associate Clinical Professor of Surgery and Attending Surgeon, New York Medical College, Flower and Fifth Avenue Hospitals; Attending Surgeon and Chief of the Soft Somatic Tissue Tumor Service, Hospital for Joint Diseases; Attending Surgeon, Pack Medical Group, New York, N. Y. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1967. 369 pages, $18.75.

The latest volume in this annual series carries forward in the tradition of the previous two volumes. It contains much of value to those interested in clinical cancer; the remainder concerns itself with new modalities of treatment and advances made in investigative procedures. The authors of each chapter have submitted a complete bibliography, of interest to the reader in obtaining further information.

The chapter, by Batson, on the Vertebral System of Veins, the importance of which he first pointed out in 1940, is beautifully illustrated and clarifies heretofore unexplained paths of tumor metastases. Dawson's excellent article on Enzyme Systems at Cellular Level is somewhat advanced and may be bewildering to the clinical surgeon, but must be read for a better understanding of the principles of enzyme histochemistry and the importance of these enzyme systems in neoplasia. The report on Cancer Trends, as determined by the Connecticut State Tumor Registry, brings us up to date on the current patterns in incidence and survival. Everson's chapter on Spontaneous Regression of Cancer is a summary from his book, in which he discusses 176 cases documented since 1900. Chapters on Seasonal Alterations of Cancer and an Epidemiological Study of Cancer in India, stress environmental factors of importance in the occurrence of this disease. New modalities, such as the use of ultra-sound in the diagnosis, and ultra-sound, the laser and the electron beams in the treatment of cancer illustrate the impact of research on specific therapeutic applications. There is a very interesting chapter on Radiographic Demonstration of Lymphatic Dynamics. The coming role of Xero-radiography as a tool in diagnosis, and its use in mammography is adequately discussed by Kossel.

There is a complete review on Ulcerogenic Tumor of the Pancreas, by Ellison, bringing all the information on this fascinating clinical entity, first described as the Zollinger-Ellison syndrome in 1955, up to date. The last part of the book contains an excellent resume of giant cell tumors and the unusual entity of mast cell disease. No treatise on cancer would be complete without a report on the Relationship of Viruses to Leukemia. The final chapter, by Novack, is on Anatomic Divisions of Cancer in the Head and Neck: The Mid-Facial Division. This site is considered a separate anatomical division for purposes of anatomy, pathology and diagnosis. The illustrations are beautifully done as are the x-ray reproductions.

All in all, the book carries on the tradition of the previous two volumes, with perhaps a little less emphasis on the clinical aspect than the average surgeon would like. It is recommended as an addition to the library of anyone interested in the diagnosis and treatment of cancer.

LOUIS SPERLING, M.D., PH.D.

* * *

TRENDS IN NEW MEDICAL SCHOOLS (A Mount Sinai Hospital Monograph)—Edited by Hans Popper, M.D., Ph.D., Dean for Academic Affairs, Professor and Chairman, Department of Pathology, Mount Sinai School of Medicine, New York, New York. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1967. 175 pages, $7.50.

This collection of essays consists of 27 papers by 33 authors. All are "concerned with ideas and problems engendered by the development of a new medical school." Major headings in the *Contents* provide evidence of the broad spectrum of topical treatment. They are: (1) Medical School — Community Relations, (2) Medical School — University Relations, (3) Problems of New Medical Schools, Here and Abroad, (4) Structures of Medical Schools in Various Countries, (5) Architecture of Medical Schools, (6) The Student, (7) Disciplines, and (8) Epilogue.

Even a superficial look at the 27 papers in these eight groupings revealed to this reviewer his own serious limitations in knowledge and insight. There is little on which he can provide substantive criticism simply because he does not know enough. There was much, however, in the several papers that he appreciated and enjoyed. To those interested in the history of medical education Professor Heilmeyer's account of the *Design of the University for Medical and Natural Sciences, Ulm, Germany*, recalls both the flowering of German medicine so well described by Abraham Flexner in *Medical Education in Europe* (1906), and *Medical Education: A Comparative Study* (1925) as well as the new world of the medical university — foretold by E. D. Churchill (New Eng. J. Med., *255*:1033, 1956) W. C. Rappleye (J. Med. Educ., *38*:899, 1963) and S. M. Mellinkoff (JAMA, *198*:629, 1966). Thus it evoked nostalgia and hope — no small accomplishment.

Dr. Grzegorzewski's poignant and vivid discussion of the problems of starting a medical school in a developing country has *déja vue* aspects for Americans. It recalls our mid-19th century days of which William Henry Welch said, "We cannot contemplate with any great satisfaction the early history of medical education in America." (Harvey Lecture, 1916).

This book contains much of value for those interested in trends in medical education. It shows the unity and the diversity of outlook of medical educators today. It is highly recommended. JOHN FIELD, PH.D.

California Medicine



The Scope and Responsibility of Medicine

A Forum with a Purpose

Many physicians and others are convinced that there is a pressing need for more discussion and more agreement concerning what ought to be the scope of medicine in today's society. At the present moment, there is no general consensus either within or without the profession. Yet if the responsibility is ever to be met, its scope must be recognized and somehow defined.

The editors of CALIFORNIA MEDICINE *propose to provide a forum in this journal for discussion of the scope and responsibility of medicine. This is a forum with a purpose, and so far as is known, an innovation in medical journalism. The forum is initiated with the statements beginning on the following page. Readers and others are invited to submit their views constructively and succinctly. As many of these as space permits will be published in future issues of* CALIFORNIA MEDICINE *as a continuation of this forum. At an appropriate time all the material will be collated and, if feasible, the distillate will be prepared in the form of a statement on "The Scope and Responsibility of Medicine" to be submitted to the Council of the California Medical Association for its consideration.*

The statements which follow are the concisely expressed views of distinguished scholars, educators, statesmen and practitioners in the health field. It is hoped their views on this timely and important subject will provoke thought and comment among the readers of this journal

Please turn the page

Reprint requests to: CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco 94102.

JOHN G. MORRISON, M.D.
San Leandro
Immediate Past President of the California Medical Association

THE SCOPE OF MEDICINE should be viewed in primary and secondary areas.

The primary range or sphere of medicine must be in its relationship to the individual—the patient who consults a physician, who entrusts the responsibilities of his health and life to a particular doctor of medicine.

In this context, one could outline the scope of medicine under five major subdivisions:

1. Bodily injuries and bodily responses to injury.
2. Disturbances of the systems of coordination and communication.
3. Disturbances of the end organ systems.
4. The techniques of medical diagnosis and therapy.
5. The art of medicine.

Under each of these major subdivisions can be included the gamut of medical knowledge in all specialties and sub-specialties.

A comprehensive understanding of the problems of clinical medicine in these five major areas is the ultimate responsibility of each doctor of medicine, the *sine qua non* for the proper application of the art and science to effect a cure or amelioration of each patient's individual and unique problem.

The secondary sphere in which medicine must be viewed is in its collective responsibility to society. This responsibility is not of medicine alone, but must relate medicine's unique knowledge in the five broad areas with many other professional groups. In this effort, medicine should share an equal responsibility in the use of its expertise with the professions of law, engineering, architecture, education, government and many others. Only in this equal cooperative effort can the goal of the broad concept of "health" for the citizens of this country be realistically approached.

JOHN H. KNOWLES, M.D.
Boston
General Director of the Massachusetts General Hospital, Boston

THE PREAMBLE TO THE constitution of the World Health Organization defines health comprehensively as a "state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity." Medicine has a long list of triumphs as regards the cure, containment, or amelioration of established somatic disease, is doing much better in some areas of mental health, but knows almost nothing of social as contrasted with biological well-being. Little attention is paid by the medical world to such causes of social disease as parental inadequacy, overcrowding, the oppressive threat of scientific war, poverty, inadequate educational opportunities, the nontherapeutic uses of leisure, the misuse of the mass media, or the suppression and persecution of minority groups. Yet, medicine today, with its successes, its problems and the demands it faces, has become inextricably a part of larger societal concerns. The obligatory inter-relationship of social, mental and somatic dis-ease (and dis-ease is stressed for clarity of meaning; that is, a lack of ease) demands a review of medicine's expanding role and suggests new functional departures.

Our teaching hospitals are called health centers today when, in reality, they enjoy a limited and exclusive function as the citadels of acute curative, scientific and technical medicine.

Medical educators speak of comprehensive medical care as including the preservation of health and the prevention as well as the cure of disease. Continuity of care and home care are stressed. Its aims are laudable but are rarely achieved today except for the "cure of disease" part. As the successes of medical science and medical technology pile up, the subdivision of medical labor increases with its attendant technical competence, discontinuity of care, manpower shortages, and high cost. These considerations coupled with the present defensive isolation of the medical world in its bastions of acute curative, specialized and technical medicine, the hospitals, prevent the giving of comprehensive care and the development of the true "health center" or a "focal point" for community health care. Obviously, our educational system and the "learning field" in medicine must be considered deficient, if its context avoids the study of social and economic dis-ease manifested, respectively, by the expanding numbers of what we call the mentally ill and by our increasing difficulty in financing the chronic care of the chronically ill as they steadily enlarge our aged population. Similarly, the availability and utilization of health services remains uneven, and those most in need, our impoverished,

our children, and our aged find themselves least able to satisfy those needs.

All roads in the community lead to the "health center" which finds itself restricted to the treatment of established somatic disease by teams of specialists. There is no public health or preventive medicine discipline available. Many hospitals have no social service and, at best, only poorly developed out-patient ambulatory clinics. There is no honest attempt to provide continuity of care or extension of services to the community and into the home. There is little coordination or communication with the other caring institutions of the community . . . the nursing homes, home-maker services, rehabilitation services, visiting nurse associations, the churches, the schools, the courts of law, urban renewal organizations . . . and the care of the mentally ill has long since been segregated and resides in distant asylums, public and private. The hospital has emerged in the eyes of the profession as the "medical center" only because of its central position in the successful treatment of somatic crises.

The health of a community must inevitably include considerations of its economic, educational, recreational, housing, and general social conditions. Somatic and psychic disease is most prevalent in urban, impoverished communities where, hand in hand, one finds the poorest living conditions, highest unemployment rates, lowest educational facilities and attainment, the greatest civil unrest. Inevitably, medicine must concern itself with the larger field of social welfare and develop a holistic concept of a community's health, if it is to prevent disease and maintain health and thereby enhance the quality of life, to say nothing of the national welfare. Such a concept will allow medicine to take its rightful place in the larger field of social welfare, and will considerably enhance the learning experience of *all* health personnel. Simultaneously, it will allow study and experimentation with the better use of scarce health personnel and the more rational use of health services by the community. The cost of such services, although absolutely increased when provided initially to such deprived communities, should be more than justified through the economic advantages of preventing disease, or of rehabilitating those with disease, to say nothing of the better use of lower cost facilities (than hospitals) where appropriate.

This is no small task for the already overburdened physician, but he must be the one who leads medicine into its expanded responsibilities.

JOHN W. CASHMAN, M.D., M.P.H.
Washington
Assistant Surgeon General, U.S. Public Health Service, Director, Division of Medical Care Administration, Public Health Service, and Health Services and Mental Health Administration, Bureau of Health Services

WHAT ARE KEY health problems facing us today? Chronic illness? Environmental pollution? Mental illness? Needless deaths and disabilities due to accidents and the preventable diseases? Yes, these, and other clinically related ones.

But what about rising medical costs, shortages of health manpower, delivery of a quality of care lower than our capacity to provide, the lack of available health care to many of our people, maldistribution of health care resources? Why are these not of major concern to medicine?

What is the business of the physician? Most of us will answer, "patient care." Few will challenge that the secret of "patient care" is in caring for the patient. The basic purpose of personal health care is to make possible the normal development of each person through the various life stages, his repair once disease has afflicted him, and the containment of his health problems which cannot be removed or reversed. The specific kind of care required to achieve this will vary. But the common need of all is continuing health guidance coupled with the provision of those services which are completely or comprehensively responsive to individual needs. This service must be met in such a way that it embodies compassionate reception and handling, and results in the effective management of whatever may be wrong with the patient.

But medical care or patient care or caring for the patient (the term in vogue now is the *delivery of comprehensive personal health services*) is more than one doctor-one patient interaction, more than the aggregate of clinical, technical and professional procedures. It involves stimulating the development of appropriate patient care institutions—hospitals, extended care facilities, nursing homes, home care agencies—and the efficient administration of them. It also includes concern about how medical bills are paid and how arrangements can be made to secure needed care of the highest quality we can provide. This is the scope and responsibility of medicine, now and for the future.

You can ask, How does one physician upgrade the quality of medical care in his community, encourage the development of the necessary health care resources, provide assurance that *all* people will have access to care, and put a lid on rising prices? Maybe one physician cannot, though I'm sure we can all agree that this is an era when one man can still put his own thumb prints on history. There are single *destructors* of our society; why can't there be single *constructors*? But whether as a "single physician" or as part of "collective medicine," you *can* influence the direction of these issues and the search for solutions.

There are many tools to assist us in improving the calibre of patient care. In the first place, there is peer judgment and review. Medical practice acts, state institutional licensing laws, the Joint Commission on Accreditation of Hospitals, Medicare's Conditions of Participation, hospital medical staff by-laws—all are standard-setting activities. Are physicians assuring leadership in setting of high standards, and, better yet, their proper implementation? Or are they just grumbling about interference with the practice of medicine? We demand performance evaluation from airplane pilots and school teachers; what about physicians? Who will take the leadership in activities designed to measure a physician's continuing competency to practice medicine? Let us hope this leadership will come from the ranks of America's private physicians and medical institutions—and that it is not left to government agencies.

What is medicine doing to assure that the consumer is getting the best buy for his dollar? Is medicine rising to the challenge of greater public accountability? Is medicine looking at utilization practices? Is medicine encouraging the most appropriate use of health care resources? Does experimentation with new types of health manpower and testing of alternative organizational methods have the full backing of the physicians? Is medicine actively and effectively exploring the scope and responsibility which it will exercise and share in the future? The answers are only faintly affirmative. A grateful public thanks those physicians who show concern in these areas and, in the context of our present health system, are helping to make the wheels turn a little more smoothly. These are the same men who are willing to sit and talk about key public policy issues—prepayment group practice, profit vs. non-profit health care facilities, fee-for-service payment, free choice of physician, new manpower explorations, and other controversial issues.

I started this brief paper with a bland question, and ended with mentioning more emotion-kindling issues—but this is the arena of modern medical care. This is what must be dealt with when we talk about caring for the patient. This is the scope and responsibility of medicine.

CHAUNCEY D. LEAKE, PH.D.
San Francisco
Senior Lecturer in the History of Health Science and Pharmacology, University of California Medical School, San Francisco • Past President, American Association for the Advancement of Science

WITH THE TREMENDOUS increase in our understanding of the causes of disease and their possible prevention, the general direction of the health profession is changing. Expanding responsibilities of members of the health professions are reflected in many reports and statements from hard-working committees of the various health professional organizations. For example, a conference under the auspices of the California Medical Education and Research Foundation was held in Chandler, Arizona, November 10 to 12 (CALIFORNIA MEDICINE 108:49-51, 1968) with over 200 physicians in attendance. In speaking at this conference on the goals and objectives of the members of the health professions, Dr. Dwight L. Wilbur, President-Elect of the American Medical Association, reported on the 11-point statement of purposes and responsibilities of the American Medical Association as adapted by its House of Delegates. This 11-point statement indicated the broad shift in responsibilities of the medical profession from exclusive concern with the care of illness or injuries in individual patients to the broader teamwork involved in promoting optimum health not only in individuals but in communities.

Medical schools all over our country are alert to the situation, as indicated by extensive study of curricular improvement. In a report to the Association of American Medical Colleges it was stated that the education of physicians must more and more include management and problem-solving rather than encyclopedic information. It was pointed out that physicians must now assume the role of team leaders having broad competence to marshal the appropriate expert knowledge and resources beyond their individual skills. Physicians

will increasingly want to know more about the methods of using, storing, and retrieving medical information, and will have to become more aware of the necessity for cooperating with health professional and service colleagues, both in patient care and in community welfare. Not only will physicians be expected to keep abreast of current scientific advances which are more and more successfully applied to medical practice, but it will also be hoped that they will promote and extend scientific and humanistic endeavor in their individual practice and in their community activity. Thus physicians will be wise to rely increasingly upon academic contacts for postgraduate refreshment both in the sciences and in the humanities.

The overall goal of promoting the optimum health for our people involves an economic factor which must be solved not necessarily by the slick conventional commercialized approaches common to our time, but rather by rendering more effective and humanized individual service, with appropriate compensation therefor. Importantly, economic factors will tend to reduce hospitalization, and thus force more responsibility for health care on clinics. Group practice is certain to expand as a result of economic pressure.

It is becoming clear that physicians are expected to be the natural leaders of the growing health teams of the future, not only in office practice, clinics and hospitals, but also in schools and other community facilities. This calls for the promotion among physicians of effective and good-willed individual cooperation with individual members of other health professions and services, who are practicing in the same community. It also suggests the wisdom of organizational liaison and interprofessional conferences.

With the extensive increase in population pressures, especially in our urban areas, there will need to be increasing attention to the emotional tensions which arise under these conditions, with resulting tendency for increasing mental disturbance which may go to social violence. Abuse of alcohol and addiction to drugs may grow and, with it, increasing responsibilities of the medical profession and its members to reduce it, by appropriate public education.

Further, in the ever-growing pollution of our environment, there must be increasing alertness to the health hazards of such pollution. The contamination of our airs and waters must be reduced, and our parks and recreational areas must be enlarged. These are social problems, but again, physicians will be expected to give the leadership that is required.

Always under the increasing pressures for satisfying health service, there will be a growing need for individual and group effort in maintaining high ideals and high standards for those giving such service. This becomes particularly difficult in the face of the flood of numbers of people who demand health care and who crowd offices, clinics and hospitals. Again, the individual deportment of members of the medical profession can set the example for all the health professions and health services. Individual members of the medical profession will be increasingly called upon to express ethical judgment on acute moral problems of practice, as in abortion, organ transplantation, euthanasia and sex relations. Here again, interprofessional cooperation will aid.

There is, then, clear indication for changing and expanding responsibilities on the part of members of the health professions. This results in part from the increasing health sophistication of our people, along with pressure from national, state and local health bureaucracies and agencies. If the members of the health professions and services can meet the challenges of the rising responsibilities facing them, they will be sure to reap rich rewards, not only from individual patients, but from society as a whole. No matter what the responsibilities for individual practitioners may be, the sense of satisfaction in attempting to meet them will help in itself to promote that good-willed cooperative endeavor toward that better health which is a worthy common goal for us all. It is to be hoped that such voluntary cooperative effort in meeting the growing responsibilities of satisfying health care will reduce and curtail the quite unsatisfactory proliferation of annoying health bureaucracies at national, state, and local levels.

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SOME DEBATES ON THE scope of medicine are more bipolar than they need be, oversimplifying the subject as though it were a television western. One side is convinced that "medicine" should be involved with the health of everyone, and therefore medical schools are too much like ivory towers, too

concerned with science and with "specialists," and a poor preparation for "practice." The other side feels that doctors and medical schools should have nothing to do with social problems or the delivery of medical care beyond individual practice. I believe that both of these views tend to camouflage the facts with linguistic confusion.

For instance, we hear some voices describing "the role of *medicine*" as if it were the role of the *physician*. While the words *medicine* and *physician* connote much that is congruous, they are by no means interchangeable. In fact, as schools of medicine have become medical universities, in response to the proliferation of discovery, the word *medicine* has come to cover a wide range of disciplines, including, for example, population genetics, hospital administration, medical economics, biomathematics, and the multiplying professions of a variety of "physicians"—family doctors, cardiac surgeons and otologists, to mention but a few. Clearly, then, the singular word *role* can scarcely apply to "medicine," and this observation is reflected not only in the curricula and concerns of medical schools today but also in medical journals so numerous and diverse that none of us can scan them all.

If it is so evident that medicine includes so many disparate fields, why, then, do we hear it argued with passion that the classic "role of the physician" is too narrow? The explanation, I think, lies not in reasoned opposition to the utter impossibility that one doctor could be an expert in more than a small fraction of "medicine," but rather in an emotional but commendable concern that none of us, insulated by our own skills or expertise, lose compassion for those members of the human family who happen not to be within our daily earshot or view. Few in medicine would oppose this motivation when stated in this manner, and its advocates include a host of the unselfish—philosophers, statesmen and martyred saints.

Therefore, if I am told that no physician can be "an island . . . every man is a piece of the continent . . . a part of the main . . .," I shall reply, "Amen." Further, if I am told that significant public affairs which require a medical perspective, such as the formulations of health insurance, should be a civic concern of physicians and a reason for us to be informed on these subjects rather than to suppose that our status justifies pronouncements *ex cathedra,* I can only agree, and point to the California Medical Association as a leader among such organizations. Similarly, when individual physicians can extricate the time to provide intelligent leadership in medically related public policy, they have my gratitude.

But there is another facet to the "role" debate. Sometimes I am told that the medical curriculum should be largely occupied with "community medicine" because "community medicine" is bigger than "individual medicine," or I am told that doctors are involved with health, and health is threatened by warfare, famine, oppression and ignorance, and therefore doctors and medical students, *as* doctors and medical students rather than as citizens of good conscience, should devote vast amounts of their inexpert efforts directly to the resolution of these ancient problems. This line of persuasion, however well-intentioned, is about as logical (and, I am afraid, sometimes as appealing) as the Music Man's pitch: "There's trouble right here in River City."

The question is not whether the world is more imperiled by overpopulation or by one child's meningitis. The question is which set of problems a particular individual is preparing himself to cope with. Political scientists, physicians, plumbers, fiscal analysts and agronomists are all needed, and as individual citizens they should be concerned with national and world affairs, but if a physician is not well educated as a physician, he will not *ipso facto* become a great sociologist.

In brief, it seems to me, we might paraphrase an ancient aphorism to read, Whereof man knoweth little, let him ask questions before making a speech.

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MEDICINE IS IN its infancy. In the long sweep of history, medicine and magic have been largely inseparable until the past 200 years. Since the turn of the century, and particularly since World War II, medicine has become a "science"—a part of human biology—but so little is really known. The great epidemics and plagues of the past are gone and the prevention and treatment of most infectious diseases in individuals has prolonged human life by more than 20 years—which has created a great many social problems for the human race. As a by-product of the control of infections came

aseptic surgery and the novel development of a large variety of reconstructive surgical procedures, including transplantation of some organs.

Paradoxically, the great success of medicine has created the most complicated and increasing demands on the services of physicians. The experiences of medical scientists and physicians have in turn led to additional knowledge, to a greater understanding of the immutable laws of biology, and to the recognition of the unique biochemical nature of each individual. While medicine and our understanding of life have become increasingly scientific, one thing seems clear: human nature does not change much, and in practicing his profession the physician must constantly keep in mind that human frailty may well overcome his scientific knowledge, skill and zeal if he does not consider the human equation in the art of medicine.

Other developments in science within medicine and without have greatly influenced it, and bear specifically on the problems of the physician and society and the scope of medicine. The control of nuclear energy, the development of effective chemotherapeutic agents in many forms for treatment of physical and mental disease, and the great discoveries in biochemistry which permit an understanding of heredity diseases, the replication of the cell, and of the individual, have broadened the scope of medicine and will continue to do so.

This broadening of the scope of medicine has greatly influenced the modern social order. It is reflected in the growth in population, in urbanization, in increased dependence of the individual on others and on a complicated social order, in longevity. It is a factor in reduced hours of work, in increased time for idleness, in early retirement, and even in a changing pattern of reproduction.

With all of these social forces at work, the economist, the sociologist, the anthropologist and particularly the politician have come into the arena of medicine. Medical research, education and service cost money—often beyond the capabilities of an individual in a modern social system in which many believe that health care has become a basic human right.

Voluntary health insurance has grown beyond all expectations, but despite this and all our affluence, government has become increasingly involved with financing of medical care—for those over 65 years of age and for those who are unable to finance it for themselves. Government, too, has played the major role in financing medical research and has assumed an increasing proportion of financing of medical education.

Nowadays, physicians, experts in insurance, in economics and in politics, as well as all the others who must have or are presumed to have individual and collective interest and responsibilities in the health field — but particularly physicians — must bring facts, expert opinion and mature reflection to bear on the crucial problems of medicine. What shall be done about the control of reproduction, qualitatively and quantitatively to maintain the best characteristics and qualities of the human race? And what *are* the "best"? What is being done about the increasing widespread use of drugs and particularly those which affect the nervous system, which make it function more efficiently, improve the memory and perhaps the intelligence, or obliterate or alter the highest functions of the brain? What about the mass use of drugs in water supplies and food? What about the moral, ethical, legal, and philosophical problems of the control of reproduction, control of genes, of DNA, of abortion, of tissue and organ transplant? Who will pay for it all and how much of our gross national product will we spend for health care, for research, for education and for care? And for what kind of research and education and care — for artificial hearts, for renal dialysis; for physicians or for those in the allied health professions and services? Who will make the decisions? More important, who will play the role of leadership which will lead to the decisions? Physicians? The medical profession? Others?

This is the scope of medicine and these are the problems of medicine.

Readers' comments are solicited. If you would like to take part in a continuation of this forum in succeeding issues of CALIFORNIA MEDICINE, *address your essays—and keep them short—to the editors of* CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California 94102.

Special Article

Gammaphotography

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■ *The Anger scintillation camera greatly broadens the range of studies performed by radioisotope imaging devices. Its ability to view in any direction, to make an image simultaneously of an entire field of view, and to obtain images rapidly, all serve to make scintiphotography analogous to fluoroscopy. Illustrations of its uses in static and dynamic gammaphotography and in numerical data processing are described.*

THE SCINTILLATION CAMERA developed by H. O. Anger at the Lawrence Radiation Laboratory and Donner Laboratory, University of California, Berkeley, is coming into sufficiently widespread use that this method of gamma radiation imaging deserves review.[1,3,4] The instrument produces a photographic image of sources of gamma radiation within its field of view. The image is formed continuously without motion of the instrument, so that stop-motion photographs or even motion pictures may be obtained. The image is referred to as a "scintiphoto" or "gammaphoto" and should be considered in some respects as similar to the more familiar radioisotope scan. Continuous imaging and the ability to obtain views rapidly while looking in any direction make the scintillation camera more analogous to a fluoroscope. The range of general clinical applications of the Anger scintillation camera as it is currently used in our laboratory is described herein.

The process of gamma-image formation by this instrument is simple in principle.[2] Gamma-rays are allowed to enter the detector only if parallel to the axis of parallel holes in the lead collimator. The gamma-rays are absorbed in a ½-inch thick, 12-inch diameter sodium iodide crystal. This converts the gamma ray energy to flashes of light at the points of absorption in the crystal. Since the crystal is relatively thin, the points of absorption are in nearly the same plane. An array of 19 photomultiplier tubes above the crystal are all exposed to the flashes of light or scintillations. The quantity of light photons "seen" by each photomultiplier tube is proportional to the distance of the tube from the scintillation. The photomultiplier tubes convert the light energy detected into greatly amplified electric pulses. The pulse sizes relative to the positions of the photomultiplier tubes are used, (to borrow a nautical term) to "take a fix" on the point at which the scintillation was detected in the crystal. This information is analyzed by a computer circuit and X and Y axis positioning signals are obtained. The process is similar to a vector analysis in electrocardiography. The positioning signals are used to produce a white dot on an oscilloscope viewing surface in the same relative position as the original radioactive disintegration. The oscilloscope is continuously photographed to accumulate sufficient numbers of these white dots to form an image. Figure 1 illustrates the major components of a camera system in the order described.

The field of view of the commercially available scintillation camera is round and of 10-inch diameter.* This size is usually sufficient to permit obtaining at a single view an image of both kidneys, or one lung or the liver. The system can analyze ten million events per minute. Because of

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*Pho-Gamma Scintillation Camera, manufactured by Nuclear-Chicago Corp., 333 East Howard Avenue, Des Plaines, Ill. 60018.

its physical characteristics, the resolution of the scintillation camera is best between gamma energies of 80 and 410 Kev, which include a wide range of clinically useful isotopes. Gamma spectroscopy allows the detection of one isotope in the presence of others. This permits use of several isotopes in one patient for sequential studies and also the differentiation of adjacent organs in single scintiphotos.

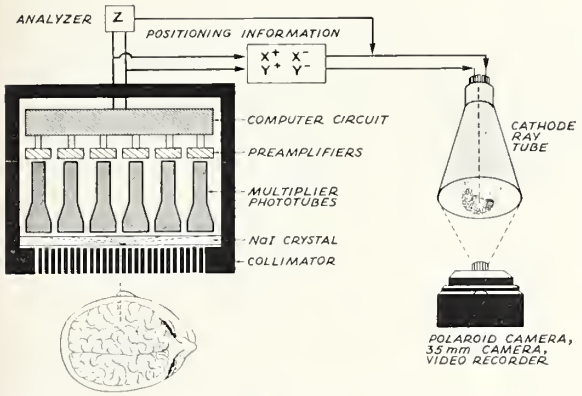


Figure 1.—Anger scintillation camera diagram. Detailed explanation of operation is given in the text. The system converts gamma-ray energy first to light energy and then to electric pulses. The pulses describe the position of origin of the original gamma-ray (X and Y pulses) and also its energy (Z pulse). The positioning information flashes the position of each event on an oscilloscope monitor only if the energy information is in the proper range, restricting the recorded image to gamma-rays of the selected energy range. The flashes of light that appear on the cathode-ray tube are collected photographically by timed exposure to form an image of the distribution of radioactivity in the subject.

As a means of further definition of the characteristics of this instrument, Table 1 provides comparison with a conventional rectilinear radioisotope scanner. It should be understood that the more familiar scanner produces a best resolved image at a depth near the focal point of its collimator. The Anger scintillation camera instead produces an image of the distribution of a selected radiation energy within its field of view, subject only to decrease by internal radiation absorption within the patient. The internal absorption results in less efficient imaging of deep parts than of those close to the detector surface. This impaired efficiency increases noticeably at lower gamma-ray energies. Figure 2 shows this effect in a commercially available liver phantom.*

The scintillation camera was the first commercial instrument generally available for gamma-imaging that produced an image smaller than the original labeled organ. Several other gamma-imaging instruments now also produce minified images. To the uninitiated viewer, these small images present some hurdles in visual psychology. Actually, more data points are produced in most of these minified images than in the previously accepted norm, the 1:1 sized rectilinear scan. Furthermore, the minimum resolution obtained with the gamma-imaging procedures in general use is between ½ inch and 1 inch, although better resolution is ob-

*Available from Alderson Research Laboratories, Inc., 48-14 33rd Street, Long Island 1, New York.



Figure 2.—Phantom studies. The plastic liver phantom was filled with a solution containing technetium 99m pertechnetate. The 1½-inch dark colored sphere contains no radioactivity. It is positioned by means of the long plastic dowel that holds it within the phantom. The gammaphoto at the left was obtained with the sphere at the surface of the phantom, the next with the sphere centered in the phantom, and the last with it at the bottom of the phantom, farthest from the camera. The depth of the phantom at this point is 4¾ inches. The phantom was photographed while under 2 inches of water, to simulate the situation of the liver *in vivo*. These photographs illustrate that surface defects are visualized more readily with the scintillation camera than are defects at a distance from the camera that are below a considerable amount of radioactive label. Because of the speed of the scintillation camera, multiple scintiphotos are obtained easily. When a large organ is studied, such as the liver, effort is made to photograph the organ from all directions, so as to optimize the probability of seeing abnormal labeling.

tainable in many studies. The most efficient image for recognition of this magnitude of resolution at usual viewing distances is about the size of the minified images. Morgan[10] and Tuddenham[13] both have discussed this point with regard to diminishing lenses for roentgenogram interpretation. Their data indicated that the most efficient viewing distance for the resolution available in conventional scans is of the order of 5 meters. Figure 3 shows the effect of image size upon spatial resolution. The effect can also be observed readily by stepping back farther while viewing the large picture. Defocusing increases apparent resolution, as is also illustrated in Figure 3, and may be duplicated by squinting while looking at a scintiphoto or by removal of eye-glasses.

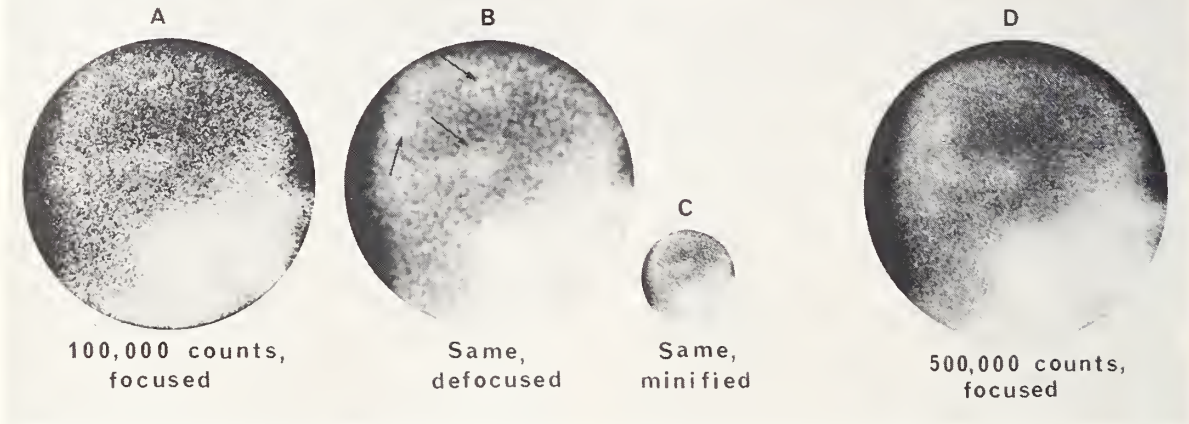


Figure 3.—Image contrast enhancement. (A) A right lateral view of the head with 100,000 dots collected in a 34-second exposure. The photograph is reproduced as originally obtained. (B) The same photograph reproduced with the dots "defocused." This increases ease of recognition of some image details. Several areas of abnormality of capillary permeability are present. (C) The original photograph reproduced in a minified image size also increases ease of recognition of details. (D) An image of the same subject obtained by collecting 5 times as many counts in a 173-second exposure. A decreased dot intensity was used in the cathode-ray tube display so as to avoid overexposure of the photographic film. This image also shows increase of contrast between target and nontarget areas and improved resolution. Arrows identify several of the definite abnormalities.

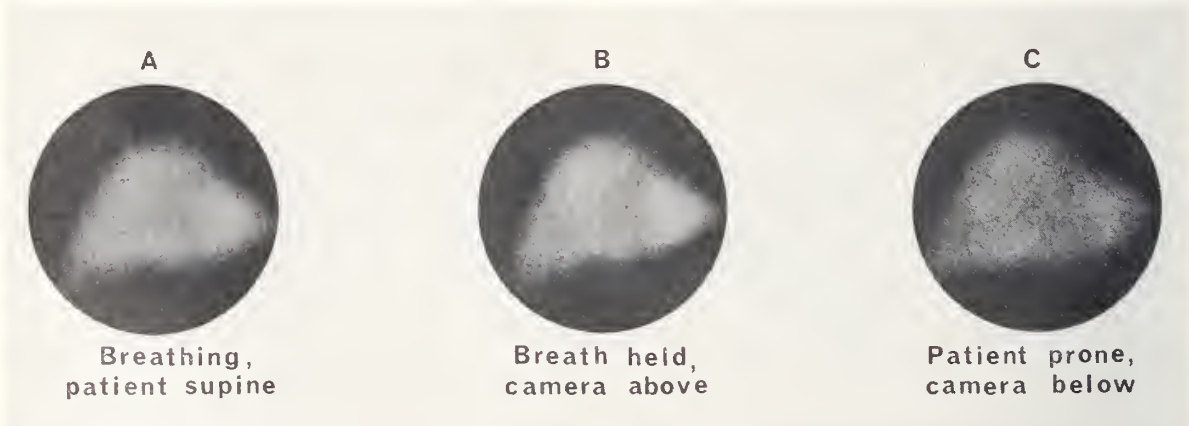


Figure 4.—Enhancement of resolution. Gammaphotos in the anterior view of a liver labeled with technetium 99m colloid demonstrate the effect of changes in camera-target orientation. (A) and (B) were obtained with the camera detector directed down at a supine patient and (C) with the detector directed up at a prone patient. Save for the change in detector-patient orientation, these anterior views of the liver are the same. During (A) the patient was breathing normally, but during (B), data were obtained only while the patient had paused in normal respiration, each pause being in relatively the same position. These gammaphotos illustrate that resolution of a mobile organ, such as the liver, is slightly increased when the photographs are obtained during cessation of respiration. Also resolution increases when this large organ is brought closer to the camera detector surface by means of placing the patient face-down with the viewing surface of the detector against the abdomen. (C) A central decrease of labeling within the liver image probably corresponds to the porta hepatis and to the large volume of venous blood in this area that is unlabeled. Minor irregularities of labeling throughout this liver image are greater than seen usually in a normal liver and may reflect some hepatocellular disease.

Clinical Scintiphotography

The principal clinical uses of the scintillation camera in our laboratory fall into three general categories: static scintiphotography, dynamic scintiphotography, and numerical data detector and processor. The organs or tissues routinely studied by scintiphotography now include the brain, thyroid and parathyroid glands, lungs, liver, spleen, bone marrow, pancreas, kidneys, joints, placenta, heart and great vessels.

Static gammaphotography is not an entirely accurate description, since many of the so-called static techniques may involve photographic exposure only when the patient is motionless. Respira-

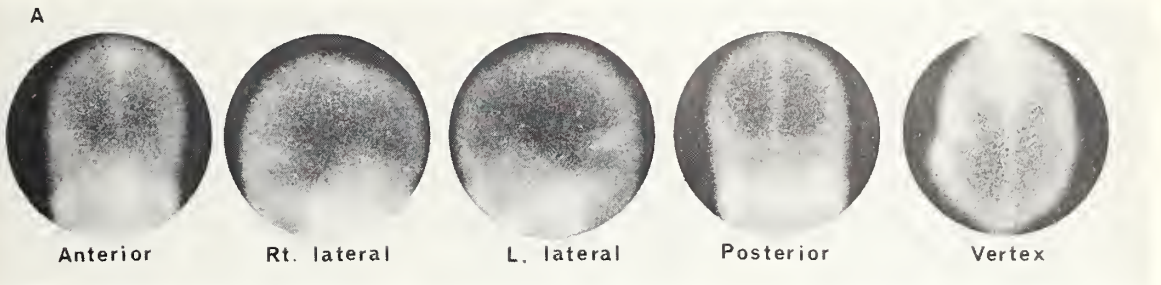


Figure 5.—Typical normal multiple view gammaphotograph studies. (A) This series of gammaphotos of a normal brain was obtained by injecting 12 millicuries of technetium 99m pertechnetate intravenously. A constant exposure time of 210 seconds was used so that all photographs would be comparable. Approximately 500,000 counts comprise a picture. Labeling in the brain areas is less than in the vascular areas since the pertechnetate does not readily pass the blood brain barrier. The superior sagittal sinus is recognized easily in the midline of the anterior, posterior, and vertex views where the camera is directed down at the top of the patient's head. For the vertex view a shield is placed over the shoulders so that the rest of the patient's body does not show in the gammaphoto. The transverse sinuses are seen joining the torcular in the posterior view and appear as bright horizontal areas of labeling posteriorly in either lateral view. Bright labeling of the salivary glands is recognizable below the brain areas.

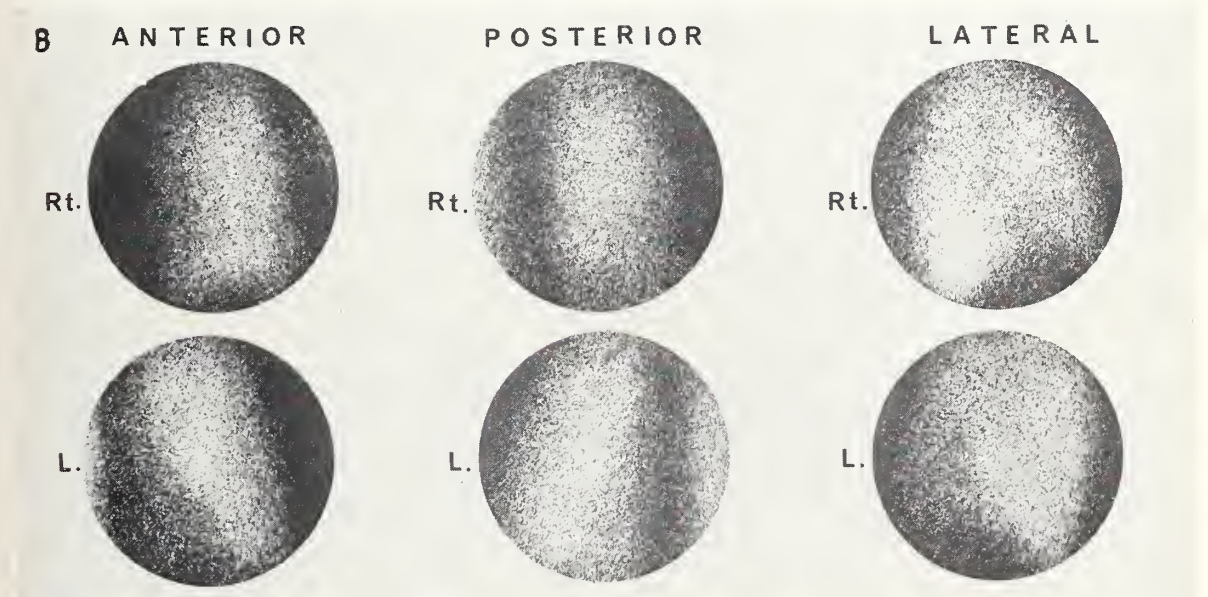


Figure 5(B).—A series of lung gammaphotos obtained again with a constant exposure time of 190 seconds to obtain approximately 80,000 counts per picture. The label is I-131 labeled macroaggregated human serum albumin which lodges temporarily in the microvasculature of the lungs and provides an opportunity to photograph the distribution of pulmonary blood flow. These lungs show fairly uniform labeling in all views, although some minor irregularities are present that are not entirely normal. This series of gammaphotos shows the degree to which pulmonary blood supply has been reestablished three months after extensive thromboembolism (note Figure 6, C). The unlabeled mediastinum and heart images are seen centrally with the outlines of the lung recognizable to either side. Because of the limited field size of the scintillation camera, each lung is photographed separately.



Figure 5(C).—Scintiphotos of normal liver showing technetium colloid distribution in the liver and spleen immediately after injection of a 3.5 millicurie dose. Again, exposure time was constant at 180 seconds in all pictures of this series. Approximately 500,000 counts were imaged in each photograph. The normal right and left lobe anatomy can be recognized and a small spleen is visualized just lateral to the left lobe of the liver. Because the spleen is a posterior organ, this anterior view does not show it well.

tory motion in conventional scans frequently causes severe motion artifacts in images of the liver and kidneys. With the scintillation camera it is possible to obtain stop-motion photographs without motion artifacts, thereby improving resolution[8] (Figure 4).

Static scintiphotos are obtained with the detector viewing the patient from as many directions as possible. As has been explained, the scintillation camera shows best resolution for the portion of the target nearest the detector. With the great sensitivity of the camera, several views are obtainable in the time required for a single view by a conventional scanner. Multiple views enhance greatly the diagnostic information available from the procedure.[7] Figure 5 illustrates a variety of the organs and tissues commonly imaged by this instrument and the various routine views.

Abnormalities in static gammaphotos are seen either by virtue of a localized increase or decrease of the expected amount of labeling within an organ. Abnormality as an increase of labeling is less frequent. It occurs with any cause of increased capillary permeability in the brain, with autonomous thyroid adenomas, in arthritic joints, and in direct labeling of malignant lesions as accomplished by Cavalieri and coworkers[6] with ^{75}Se selenite. More often, scintiphoto abnormalities are seen as decreased labeling in a labeled lung, liver, spleen, kidney, pancreas or thyroid gland. Figure 6 illustrates some typical abnormal static scintiphotos with both types of abnormalities represented.

Dynamic scintiphotography — that is, "stop-motion" or "time sequence" photography — is obtained with the scintillation camera. For this purpose, the exposure times and other photographic characteristics are constant for a series of scintiphotos with a constant camera-patient orientation. Such scintiphotos allow evaluation of changes of isotope localization as a function of time. They may be used to follow labels in the circulatory

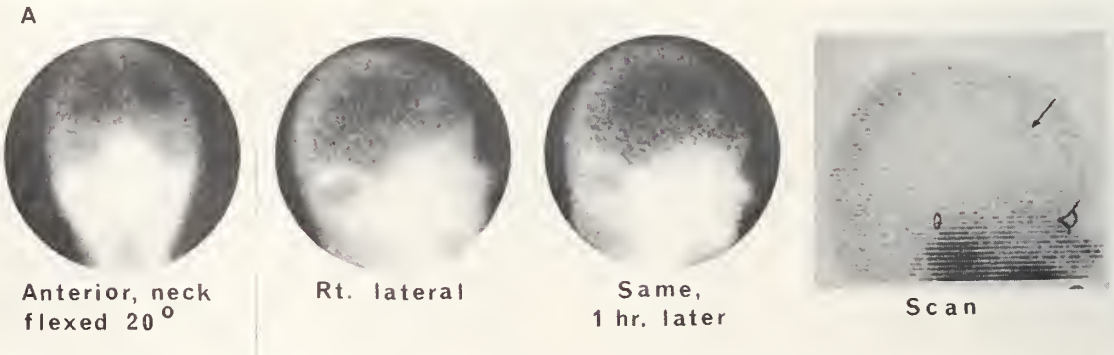


Figure 6.—Abnormal static gammaphotograph studies. (A) Abnormality of capillary permeability of brain (arrow) shown here is considered to be the result of arterial sclerotic cerebrovascular disease. A conventional rectilinear scan using a fine focus collimator positioned for the known depth of the abnormality provides for comparison of the gammaphotographs with the more generally understood scanning technique. The abnormality is just visible in the scan.

system, in the airways, during renal excretion, during secretion of dye by the liver, and in many other processes.[5,9,11,12]

The amounts and the volumes of labeled pharmaceuticals are physiologic. Therefore, the data provided by dynamic scintiphotography tend to be physiologic as opposed to those with nonphysiologic doses of radiopaque dyes and a variety of conventional roentgenographic procedures. Figure 7 illustrates some abnormal dynamic scintiphoto studies.

The interest in dynamic scintiphotography has been paralleled by that in the scintillation camera system as a numerical data detector and processor. The commercially available scintillation camera is equipped with a built-in simple data processor. Operation with an electronically divided field of view allows separation of counts from each kidney or from each cerebral hemisphere. The data may be further processed by operation in a preset time mode with automatic cycling so that data are counted from each half of the field of view for the

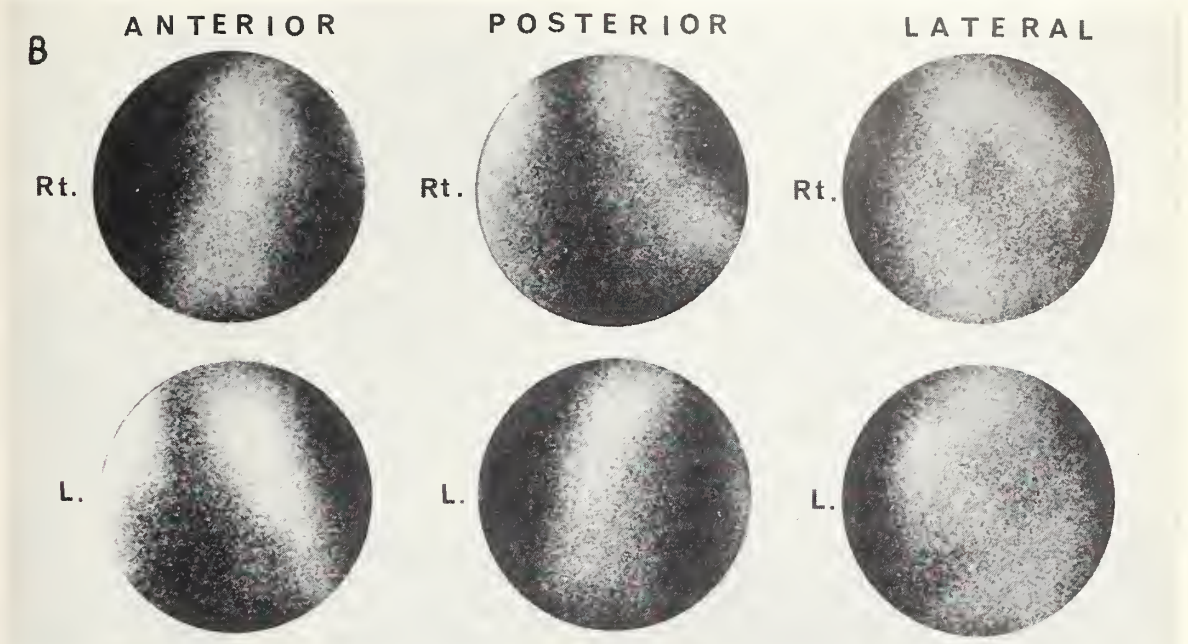


Figure 6(B).—Focal abnormalities of patterns of pulmonary arterial perfusion are seen in several areas in these lungs. These abnormalities are caused by thromboembolism, but similar defects of perfusion might be seen when the lung is displaced by tumor or blebs, or when pulmonary arterial perfusion is decreased by other causes, notably bronchogenic carcinoma, congenital anomalies, and involvement in pulmonary fibrosis.

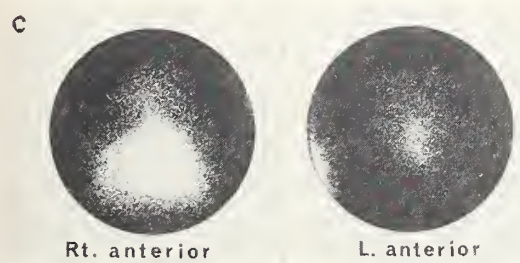


Figure 6(C).—Emergency gammaphotos of the lungs were obtained with I-131 labeled macroaggregated albumin. The result of massive pulmonary thromboembolism is illustrated. This patient was too ill to undergo further views. The exposure time for each of these views was 231 seconds. Because of the positioning mobility of the detector, these studies can be obtained in a sitting position. These grossly abnormal gammaphotos eventually showed clearing, with nearly normal scintiphotos (Figure 5, B) resulting three months after these emergency gammaphotos.

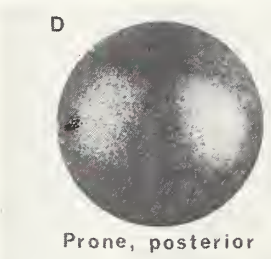


Figure 6(D).—A posterior view gammaphoto of Hg-203 chlormerodrin-labeling of kidneys. The left kidney appears somewhat smaller and less well labeled than the right. Significant hypertension is present in this patient and the left kidney is known to be involved with fibromuscular hyperplasia causing renal ischemia. The right kidney is imaged somewhat lower in position than is usual with the patient prone, owing to surgical fixation two years previously for fibromuscular hyperplasia of the right renal artery. This gammaphoto required 900 seconds and there are 39,000 counts in the right half of the field of view and 28,000 in the left half, a measure of the discrepancy in the amount of labeling in either kidney.

preset time interval, printed on paper tape at an extremely rapid rate (30 lines per second), and the process recycled. Figure 8 (A) shows a hippurate renogram obtained in this manner. A further refinement, but similar in principle, would be the ability to specify electronically that numerical data would be obtained from a defined area of the field of view—for example, from just the area representing one kidney. This is in essence what may be done with digital data processing. Such numerical processing allows compensation to make response uniform from all areas of the detector, subtraction of data (one organ image by one label from this organ's image, plus a second organ by a second label to show only the second organ), extraction of area counts per unit time, and many other maneuvers. Figure 8 (B) shows scintillation camera data in a multichannel analyzer display.

The strength of analyzer-processed data lies in the speed and convenience of processing digital

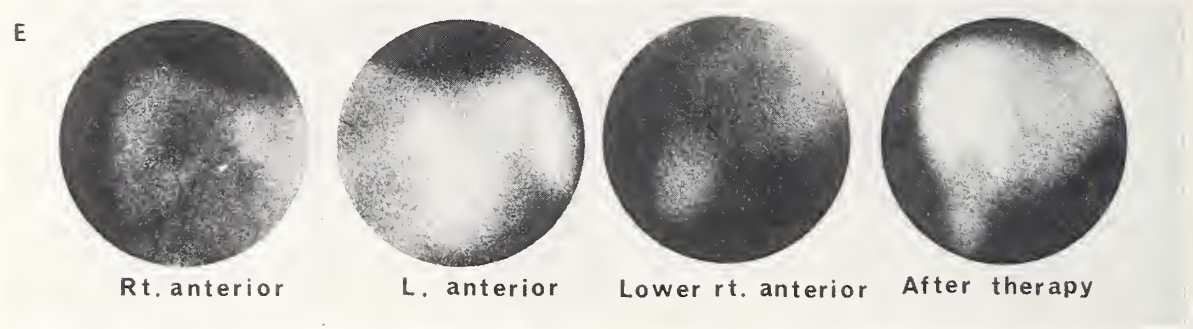


Figure 6(E).—This series shows abnormalities of liver labeling in an enormously enlarged liver, shown in three separate anterior views. The abnormalities resulted from metastatic seminoma. After chemotherapy and radiation therapy the gammaphoto at the right shows considerable improvement of the liver image with much more uniform labeling, and a marked decrease in its size to nearly normal.



Figure 6(F).—These anterior views of polycystic liver disease show what can be accomplished by composite of several gammaphotos when a grossly enlarged organ does not fit into one camera field of view.



Figure 6(G).—Gammaphotos of the pelvis show increase of marrow labeling and extension of marrow into the right mid-femur, consistent with marrow hypertrophy. Marrow does not normally extend as far distally.



Figure 6(H).—These gammaphotos were obtained shortly after injection of 10 millicuries of technetium pertechnetate and show arthritic involvement of peripheral joints. A striking symmetric involvement of the fourth phalangeal-metatarsal joints is seen and increased labeling is distributed with less symmetry in other joints. The right third proximal interphalangeal joint of the hand and the right first metacarpophalangeal joint are the only ones involved in the two-hand gammaphotos. This patient had rheumatoid arthritis.



Figure 6(I).—Gammaphotos of the thyroid and a conventional thyroid scan are compared. In these gammaphotos the thyroid was relatively enlarged compared with the sizes of the images in the other gammaphotos, because a different collimator was used. This single pinhole collimator produces the relatively larger images when the pinhole is close to the target and relatively smaller when it is farther away. By obtaining pictures with the pinhole close to the thyroid, the whole field of view is filled by the image. In the 5,000-count anterior and right anterior oblique views, the gammaphotos show increased labeling in the lower pole of the right thyroid lobe. Just above and lateral to this area is one of decreased labeling, better seen in the anterior oblique than in the anterior view. The 25,000-count anterior view defines the distribution of radioiodide somewhat better than did the previous picture. The scan also shows essentially the same findings with better labeling by radioiodide of the lower pole of the right lobe than elsewhere. A cold nodule above and lateral to this area of relatively greater uptake is poorly defined.



Figure 7. — Dynamic gammaphotograph studies. (A) This sequence of 4-second exposures was obtained after peripheral intravenous injection of 12 millicuries of technetium 99m pertechnetate. The camera images an anterior view of the patient's head. In the 4-second and the 8-second gammaphotos are seen patterns of the carotid artery, middle cerebral arteries, and anterior cerebral arteries plus the midline vasculature. Labeling of the right carotid artery pattern is less than of the left, indicating that the flow through this vessel is less. In the 12-second scintiphoto, bright labeling is seen of the superior sagittal sinus and also of the midline vascular structures. Thereafter, the image of the superior sagittal sinus fades away. No abnormal labeling is seen within areas of the brain hemispheres to suggest any sort of a vascular abnormality.

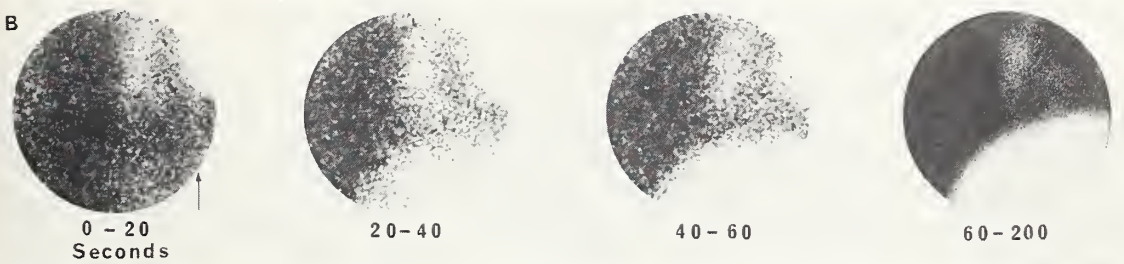


Figure 7(B).—This series of scintiphotos shows an interesting and as yet undescribed technique for demonstrating pleural and pericardial effusion. The patient is studied in the upright position with the camera visualizing the heart and the right hemidiaphragmatic areas. An injection of technetium 99m colloid is given and a series of 20-second scintiphotos is obtained, using bright dots. These show in the first 20 seconds the labeling of the right heart chambers and the pulmonary blood flow in the base of the right lung. A faint image of the abdominal aorta is seen below the heart. The next gammaphoto in exactly the same position shows a marked increase in labeling in the liver area with some decrease in the lung and heart areas. In the third photo between 40 and 60 seconds, the liver labeling has progressed. The distance between the right ventricle and the liver and the right ventricle and the lung is somewhat increased over normal and is consistent with the effusions in the pericardium and the pleural space. The diagnosis here was widely metastatic seminoma. A late gammaphoto using accumulation of a much greater number of dots over a prolonged exposure with diminished dot intensity shows in the same position a residual labeling of the base of the right lung and the labeling within the liver.

data. The weakness is that data are no longer "real time"; they are processed by batches accumulated over a time interval and each batch must be transferred onto magnetic tape for later processing. The transfer of a buffer content (that is, a batch) requires appreciable dead time, limiting the minimum time period for dynamic data acquisition by a single buffer to 1 or 2 seconds. This limitation can be avoided by recording in real time on videotape. When the video tape is played back, the light energy flux from a defined area of a monitor oscilloscope may be detected by photomultiplier tube and recorded by strip chart. Other areas similarly recorded are all on the same time base and may be compared as parallel analog data. Figure 8 (C) shows this variety of data processing by scintillation camera.

No mention has been made of data processing

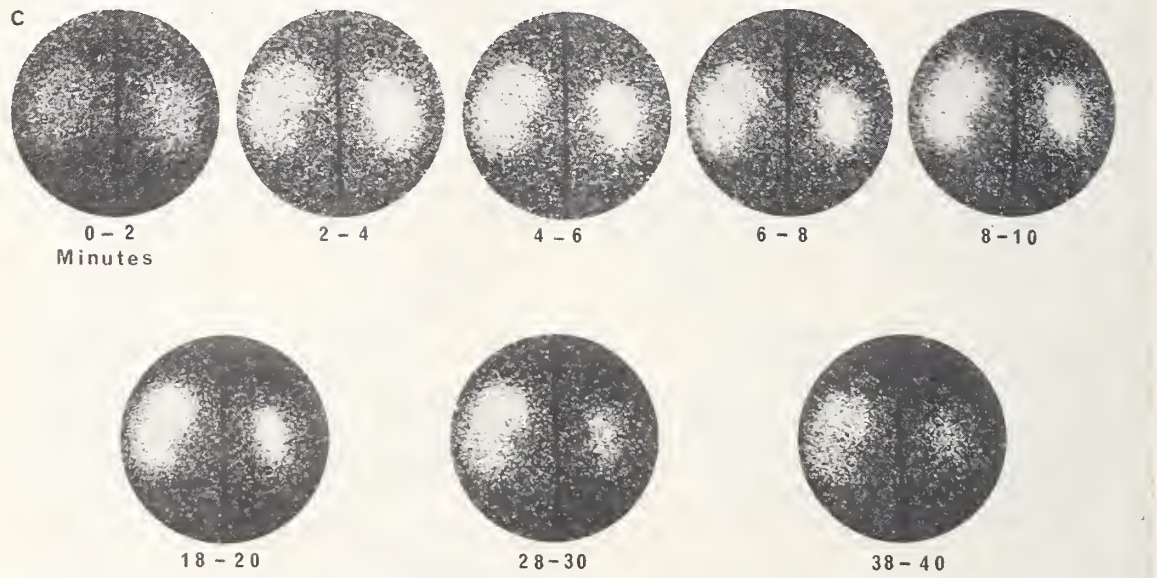


Figure 7(C). — A posterior view gammaphoto of the same patient of Figure 6, D. I-131 hippurate was injected and a series of scintiphotos was obtained in exactly the same position as the previously illustrated Hg-203 chlormerodrin picture. The right kidney is seen to accumulate the hippurate rapidly and drain the hippurate into its central or pelvic area. The label is then lost from the field of view of the camera because of drainage into the ureter and the bladder. The left kidney is seen to accumulate the hippurate at a slow rate and also to retain the label within the renal image to times when label should have cleared the kidney. The label, furthermore, is out in the renal cortex on the left and there is no evidence of an obstructive process involving the left renal pelvis. The reason for the delay of the excretion of the hippurate is an increased water resorption and a decrease of urine volume. This causes the late apparent "hyperconcentration," commented upon in various pyelographic studies, and is similar to the abnormalities defined in renovascular hypertension by the Stamie-Howard test. The advantage of gammaphotography is its ability to define regional renal function as opposed to function of an entire kidney, as would be defined by a radioisotope renogram or the Stamie-Howard test.

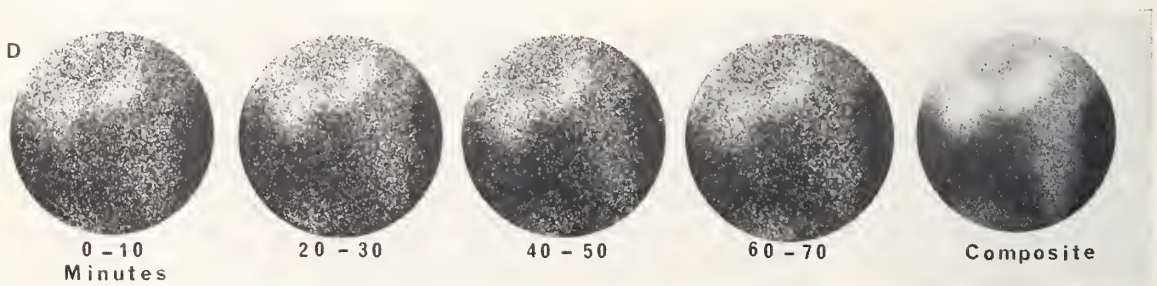


Figure 7(D). — This series illustrates pancreatic labeling by utilization of ^{75}Se methionine for resynthesis of pancreatic enzymes after pancreatic exocrine secretory function has depleted these enzymes. Illustrated is a perfectly normal pancreas with the head and tail well defined and separated by a defect caused by the impression of the abdominal aorta across the posterior surface of the pancreas. Changing amounts of labeling often can be seen in such a series of scintiphotos as enzymes are synthesized and secreted. The last picture is a photographic composite of eight preceding exposures, showing approximately 500,000 counts in one pancreatic scintiphoto. The abdominal musculature is seen in the left flank and labeling is seen above the pancreatic image where uptake has occurred in the liver.

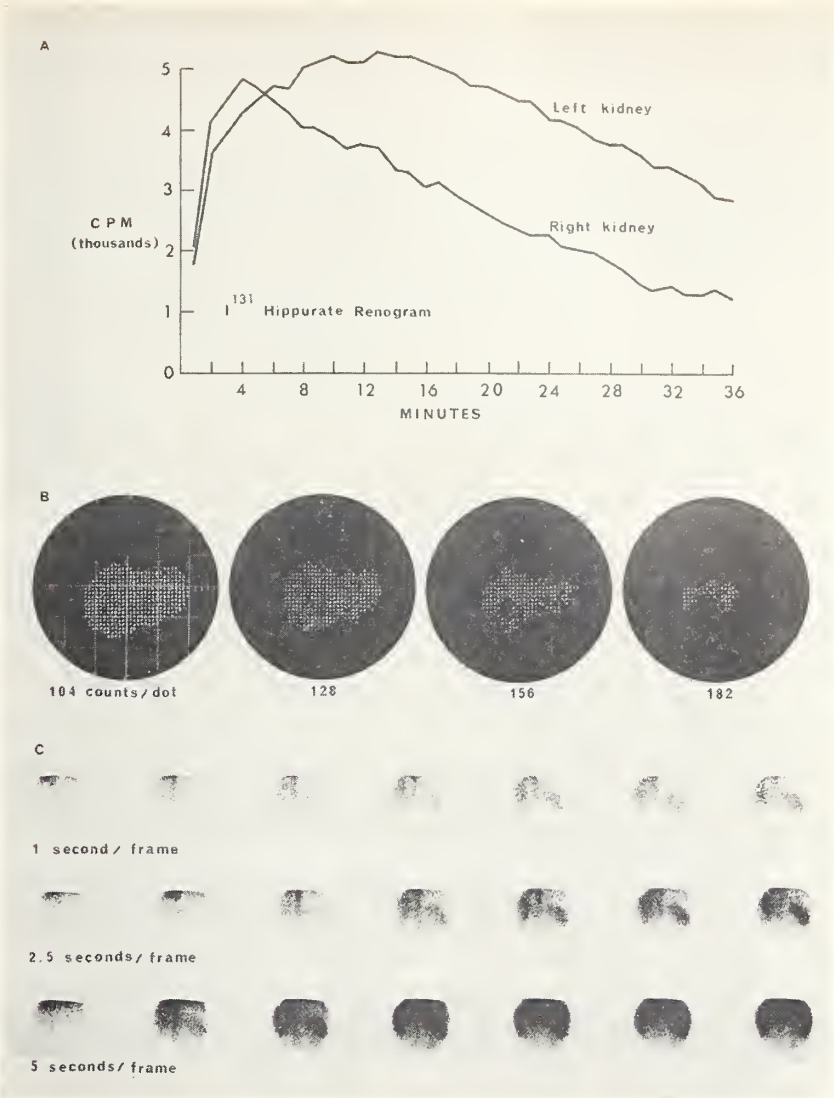


Figure 8.—Scintillation camera data processing. (A) This hippurate renogram was obtained with the scintillation camera by plotting numerical data recorded by a rapid printer from each half of the camera field of view. The count-rate over the right kidney follows a normal course with rapid accumulation of counts in the first four minutes because of labeling of the renovascular blood pool and then by tubular function with concentration of the hippurate in the renal tubules. Following this the count-rate peaks at four minutes and the drainage phase is normal for this type of renogram and patient position. The left kidney tracing is abnormal with a slower accumulation of counts, a broad delayed peak, and retention of counts in the kidney. This sort of curve could be reproduced by obstruction to ureteral drainage, but this is the renogram obtained simultaneously with the scintiphotos in Figure 7 (C) and these demonstrated that the retained counts are in the renal cortex. Drainage from the left renal pelvis was not delayed, as would occur with obstruction. Therefore, this renogram represents a prolongation of hippurate transit time, the result of increased water resorption in the cortex, and is consistent with the diagnosis of renovascular hypertension. (B) Static gammaphotos showing data-processing by a multichannel analyzer. A 4096-channel analyzer* was used to display the number of counts per area in a 64 x 64 array of analyzer positions. If a dot is illuminated, it indicates a given number of counts per area at that position. The number of counts represented per dot is labeled in the illustrations. The image shown is the liver phantom illustrated in Figure 2. As the analyzer is adjusted to show increasing numbers of counts per channel, the defect caused by the dark-colored sphere in the center of the phantom becomes visible. This analyzer data manipulation is what might be referred to as "electronic dissection of gamma anatomy." (C) Gammaphotos of renal blood flow with technetium 99m pertechnetate injected into a peripheral vein. The data from the scintillation camera were recorded first by video tape. The video tape was played back and 35 mm photographs were obtained at a rate of one per second, one per 2.5 seconds, and one per five seconds, showing the effect of changes in exposure time on image density in these dynamic studies. The blood-flow pattern in these kidneys was normal.

*Nuclear Data Inc., 100 West Golf Road, Palatine, Ill. 60067.

TABLE 1.—*Comparison of Gamma Imaging Instruments*

Function	*Conventional Scanner*	*Scintillation Camera*
Collimation		
Holes in lead absorber; gamma-rays from selected angles pass through holes; other gamma-rays absorbed in lead.	Holes converge to a focal point 3 to 5 inches beyond detector.	Holes are parallel and perpendicular to the detector plane.
Energy Conversion		
Crystal: NaI with thallium seeding absorbs gamma-rays, converts gamma energy to light (scintillation) at points of absorption.	3-inch or 5-inch diameter x 2 inches thick: better efficiency of gamma absorption	12-inch diameter x ½ inch thick: keeps scintillations nearly in same plane.
Multiplier phototubes detect light energy, convert and amplify as electrical pulse.	One	Nineteen, in an array to "take a fix" on each scintillation
Image Formation		
Information positioned in image by	Mechanical link of detector and image formation unit to record an area point by point.	Electronic computation of position, display on cathode-ray tube to continuously record whole area.
Gamma image recorded by	To and fro motion of dot tapper; small light source to expose x-ray film.	Photographic recording of continuous display on cathode-ray tube.
Result		
Image size	Life size, 1:1.	Miniature, 1:8.
Image type	Tap scan: rows of black taps. Photo scan: rows of grey to black film exposures.	Polaroid: white dots on black background. Conventional film: black dots on clear background.
Data density in image (compared with time for image formation).	Low	High
Speed	Low—used primarily for static studies.	High—sufficient for dynamic studies, e.g., blood-flow imaging.
Miscellaneous		
Field of view	To 14x17 inches, rectangular.	10 inches, circular.
Direction of view	Usually down; up in a few models.	Any
Useful energy range	25 to 520 Kev.	80 to 410 Kev (can be extended to 510 Kev by special collimation).

by collimation. Obviously, shielding of part of the detector holes with lead can block unwanted data from the camera. The field of view of the camera may be enlarged by changing the collimation; divergent collimator holes with a negative focus would enlarge the field of view, as will the single pin-hole collimator that is at present available with the commercial camera. This collimator functions like an old-fashioned box camera, with image size inversely proportional to distance between subject and camera.

The future development of the scintillation camera will no doubt lie in the area of data processing and larger detectors. The positron detecting scintillation camera, which is now becoming available, will extend the range of isotopes which the instrument can image.

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REFERENCES

1. Anger, H. O.: Gamma-ray and positron scintillation camera, Nucleonics, 21:56, Oct. 1963.

2. Anger, H. O.: Radioisotope cameras, *in* Hine, G. J.: Instrumentation in Nuclear Medicine, Vol. 1, Academic Press, New York, 1967, pp. 486-552.

3. Anger, H. O., Powell, M. R., Van Dyke, D. C., Schaer, L. R., Fawwaz, R., and Yano, Y.: Recent applications of the scintillation camera, Strahlentherapie (Sonderb.), 65:70, 1967.

4. Anger, H. O., Van Dyke, D. C., Gottschalk, A., Yano, Y., and Schaer, L. R.: The scintillation camera in diagnosis and research, Nucleonics, 23:57, Jan. 1965.

5. Burke, G., Halko, A., and Coe, F. L.: Dynamic clinical studies with radioisotopes and the scintillation camera. I. Sodium iodohippurate I-131 renography, JAMA, 197:15, 4 July 1966.

6. Cavalieri, R. R., Scott, K. G., and Sairenji, E.: Selenite (^{75}Se) as a tumor-localizing agent in man, J. Nucl. Med., 7:197, Mar. 1966.

7. Gottschalk, A.: Radioisotope scintiphotography with technetium 99m and the gamma scintillation camera, Amer. J. Roentgen., 97:860, Aug. 1966.

8. Gottschalk, A., Harper, P. V., Jiminez, F. F., and Petasnick, J. P.: Quantification of the respiratory motion artifact in radioisotope scanning with the rectilinear focused collimator scanner and the gamma scintillation camera, J. Nucl. Med., 7:243, Apr. 1966.

9. Loken, M. K., and Bugby, R. D.: Visualization of the lung by methods of scintiphotography, Amer. J. Roentgen., 97:850, Aug. 1966.

10. Morgan, R. H.: Visual perception in fluoroscopy and radiography, Radiology, 86:403, Mar. 1966.

11. Powell, M. R., and Anger, H. O.: Triple isotope renal evaluation with the scintillation camera, J. Nucl. Med., 7:373, May 1966. (Abstr.)

12. Powell, M. R., and Anger, H. O.: Blood flow visualization with the scintillation camera, J. Nucl. Med., 7:729, Oct. 1966.

13. Tuddenham, W. J.: Visual search, image organization, and reader error in roentgen diagnosis. Studies of the psychophysiology of roentgen image perception, Radiology, 78:694, May 1962.

Salivary Gland Tumors and Sialadenitis In Children

Experience at Childrens Hospital of Los Angeles

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■ *Parotitis, hemangio-endothelioma and mixed tumors are the most common salivary gland lesions in the pediatric age group. Carcinoma and sarcoma are uncommon. Rapid growth of a tumor and pain suggest malignant change.*

A conservative non-operative approach is stressed for most cases of chronic parotitis. Scout x-ray films and sialangiographic examination are useful in differentiating an inflammatory lesion from a neoplastic growth. Total parotidectomy is advised if operation is indicated.

A case of spontaneous resolution of a hemangioma of the parotid gland is presented. A less aggressive temporizing plan should be considered with these lesions, as the risk of seventh nerve injury in children is considerable.

The treatment of choice for a non-inflammatory tumor is surgical excision, for most parotid tumors are radioresistant. Small masses should be completely excised for pathological evaluation. Incisional biopsy may occasionally be indicated in the case of a large diffuse lesion, for it may be inflammatory and total excision unnecessary. Most patients with chronic parotitis came to medical attention because of a non-tender asymptomatic parotid lump or diffuse swelling.

EXCLUDING MUMPS, 71 patients with major salivary gland problems were admitted to the Childrens Hospital of Los Angeles from 1948 to 1966.[11] It was noted that, except for obvious inflammation or infectious parotitis, the major reason for seeking medical attention was the presence of a non-tender, asymptomatic parotid lump or swelling.[2]

Most lesions of the salivary glands in the pediatric age group are of the acute and chronic inflammatory variety. They may be initially asymptomatic and grow slowly and insidiously.

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Non-inflammatory parotid tumors are seen in newborn babies and infants, but are more common in older children. The hemangioma-endothelioma and mixed tumor are the most prevalent. However, fewer than 3 percent of all mixed tumors occur in this age group.[1,3,10,17]

More than 8 percent of all tumors in children are in the head and neck area[18] (if tumors of the brain and eye are excluded). The skin, nasopharynx, thyroid and salivary glands are the most common primary sites. Lymphomas, neuroblastomas, and reticuloendothelioses are common secondary lesions in this area.[4]

Recent Series

There were 45 cases of acute or chronic parotitis seen at Childrens Hospital in the period 1948 to 1966 (Table 1). Cases of mumps were excluded and patients with that disease were discharged to the infectious disease ward at the Los Angeles County Hospital or to their homes.

Twenty-one cases of chronic parotitis were reviewed. In only six of the cases was biopsy performed and none of the patients had parotidectomy. The clinical course and sialograms indicated conservative therapy with antibiotics and observation as the rule. In four cases, both sides were involved and, in general, there was no predominance of one side. The age span was from seven months to 18 years. The most common symptom was an asymptomatic, firm swelling which was recurrent in several cases. In all patients except one, the lesion subsided with time.

There were 24 cases of acute parotitis, of which two were postoperative. The majority occurred in males and the right side was involved twice as frequently as the left. Staphylococcus aureus was the predominant offender, followed by streptococcus viridans and pneumococcus. Two newborns and seven additional infants less than one month of age were affected with this problem. The common factor in the children less than one month of age appeared to be dehydration secondary to diarrhea, vomiting or other factors leading to dehydration or cachexia. In nine of the 24 cases of acute parotitis incision and drainage were necessary because of fluctuation and pointing, and in four of the nine cases the patients were less than one month of age. No further therapy or operation was required in any of this group.

Hemangioma

There were seven cases of parotid hemangioma in this series and all were in girls. The tumor was detected either at birth or during the first few months of life. Four children had parotidectomy, and of these one had persistent facial nerve palsy; one patient was treated conservatively for a parotid hemangioma which had been noted when she was less than one year of age. Ligation of the external carotid artery, radiation therapy and subsequent injection of sclerosing solutions were carried out. A 3 cm mass was still present in this patient at 11 years of age.

Another child presented with an 8 cm parotid hemangioma and was treated with irradiation, 300R. The lesion decreased 30 percent in size in one year, and the remainder probably will be resected soon. One child had a parotid hemangioma 3 to 4 cm in diameter (Figure 1) present at birth, with skin involvement. The lesion completely regressed without therapy within three years.

TABLE 1.—*Major Salivary Gland Disease in Children. Etiologic Findings in 107 Cases at Childrens Hospital, Los Angeles*

Mumps (excluded)	36
Chronic Parotitis	21
Acute Parotitis	24
Submaxillary Gland Sialadenitis	14
Tumors	5
Hemangiomas	7

Submaxillary Gland

Fourteen cases of submaxillary problems were reviewed. All of the lesions were of an inflammatory nature and no neoplastic growths were detected. Three sublingual gland cysts were marsupialized into the oral cavity. One 11-year-old child had removal of a calculus from Wharton's duct. Five children had incision and drainage for a submaxillary abscess and two had excision of the gland for what appeared on sectioning to be an infectious granulomatous inflammation. One patient had biopsy only for diagnosis.

Parotid Neoplasms

Five cases of parotid neoplasm were reviewed.

Case 1.—A six-year-old boy was admitted in January 1961. He had noted a swelling in the right parotid region for one month. Total parotidectomy with sacrifice of the seventh nerve was performed soon afterward for a malignant mixed tumor with neurofibrosarcoma as the major element. Postoperative treatment with 1,650 roent-



Figure 1.—3-4 cm hemangioma in a child. Complete resolution within three years.

gens was given in March 1961. The patient died at home in November 1961 with extensive involvement of the face and oral cavity.

CASE 2.—An 8-year-old boy was admitted in October 1951 with a 4 cm mass in the right parotid gland. The tumor was resected and the area was treated postoperatively with radiation. The tissue diagnosis was malignant mesenchymal tumor. The child died six months later of extensive local disease.

CASE 3.—An 18-month-old girl was admitted in July 1946 with a 1 cm mass in the right parotid area. There were *cafe au lait* spots over the body. Over the next three years the tumor enlarged to involve the right cheek and ear. In 1949 a large portion of the mass was excised. After operation the patient had a facial palsy, which persisted. The pathologist's report was "plexiform neurofibroma with a sarcomatous pattern." The patient has since had more than ten re-excisions and plastic corrections. She is now 20 years of age, is free of disease, and married with one child.

CASE 4.—A 15-year-old girl had subtotal parotidectomy in February 1958 for a 2 x 3 cm firm mass below the right ear lobule. The diagnosis was a benign mixed tumor of the parotid. She is now nine years postoperative without evidence of recurrence.

CASE 5.—A 5-year-old boy began to have swelling in the right parotid area several weeks before admission. Paralysis of the lateral rectus muscle of the right eye was also found. Biopsy of the pterygoid area disclosed a rhabdomyosarcoma. The child is now receiving radiation therapy to the affected areas and systemic actinomycin D.

Acute and Chronic Parotitis

The most common problem in analyzing parotid swellings is the differentiation of inflammatory lesions from neoplasms. Most of these lesions are asymptomatic, diffuse, and (usually) unilateral. Parotidectomy for parotitis is a difficult procedure and the difficulty becomes magnified in infants or children because of associated risk to the seventh nerve.

Acute parotitis is usually easily diagnosed when the classic findings of an inflammatory process are present. One may find tenderness, pain, swelling, erythema, fever, purulent drainage from Stensen's duct and systemic reactions such as debility or malaise.

Acute parotitis is seen most frequently after infections about the head and neck, after general infectious diseases with septicemia and pyemia, after dehydration and cachexia, following operative procedures, and in the course of chronic parotitis. It is usually the result of an ascending infection from the mouth and the most common offending organisms are staphylococci, streptococci and pneumococci.

It is important to obtain a culture of material from the parotid duct and to get accurate identification and drug sensitivity studies as soon as possible. As the offender is staphylococcus in most cases, an anti-staphylococcus drug in full therapeutic dose should be started immediately and a change made if necessary when sensitivity studies are back. The treatment also consists of local hygienic measures and application of compresses.

If conservative measures have not controlled an obviously progressing disease with increased pain and swelling within 72 hours, immediate surgical drainage should be considered.

Care should be taken to determine whether the parotid swelling is the first such instance or is a recurrent flare-up of inflammation. The swelling may subside at the end of an attack in chronic parotitis or there may be some persistent enlargement with a history of recurrences. The attack may last from a few days to weeks and may recur at intervals of weeks to months. It is more frequently seen in children than in adults, but may be found at any age. Fever, anorexia and malaise are usually of a mild degree in chronic parotitis. The presenting complaint is, in most cases, an asymptomatic diffuse swelling in the parotid area.

Persistent swelling usually represents a later stage of the disease, with chronic inflammation and dilated cystic areas and ineffective drainage of retained secretions. Roentgenographic studies rarely show parotid calculi.

Sialadenography[22] (Figure 2) may help to establish the diagnosis (Figure 3). General anes-

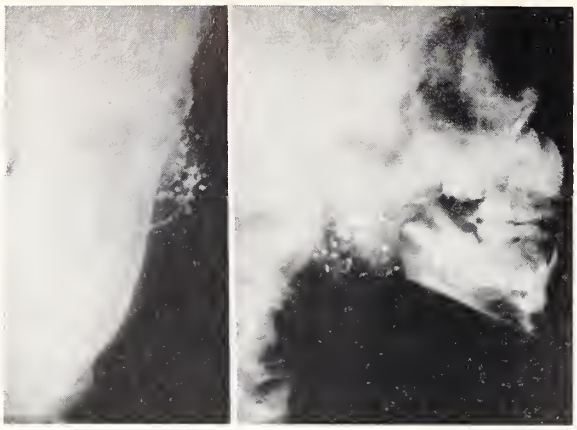


Figure 2.—Sialogram of a child with chronic parotitis.

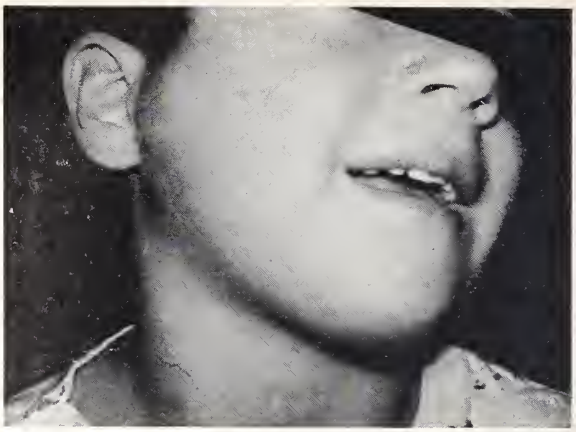


Figure 3.—Tumor of chronic parotitis in a 7-year-old boy.

thesia is required unless the infant or child can be managed under sedation. A small lacrimal cannula is inserted into the Stensen duct orifice and about 0.5 to 1 ml of a warm solution of contrast medium (Lipiodol®) is injected slowly. In most cases either a normal ductal system or sialangiectasis with a classic beaded appearance as in bronchiectasis will be demonstrated. The latter is diagnostic of chronic parotitis and usually in such cases the lesion will take more dye than a normal gland. The sialogram will also demonstrate an intra or extraglandular growth that is causing pressure on the ductal system. Its major value is in studying a parotid disease process without an obvious diagnosis.

The etiologic factor is not known but the common cause is thought to be ductal obstruction and secondary infection. The causative organism varies but staphylococcus and streptococcus viridans are frequently implicated.

Poor oral or general conditions, mucosal atrophy and glandular abnormalities may all be present. Glandular involvement may be a part of a secondary process from a generalized disease—for example, sarcoidosis lymphoma, or tuberculosis. Allergic disease and sensitivity to drugs have been incriminated in children.[15] Some of the drugs which may cause parotitis are mercury, lead, copper, iodine, nicotine and opium. Among food substances, spinach, pork, lemons, grapes, oranges, acidic foods, iodized salt and tuna fish have been implicated as a cause.

A second episode of swelling of the parotid gland followed by a period of quiescence suggests a chronic process, and a thorough investigation should be made to determine the cause. Ductal secretions should be cultured, if possible. Probing of the duct orifice is not advised.

In the majority of cases of chronic parotitis, the disease will subside without an operation.[5] An appropriate antibiotic should be used in full dosage over a period of three weeks if a causative organism and sensitivity are determined.

Specific treatment is instituted for any structural abnormality, stricture or calculus. Oral and dental hygiene with mouth washes, passive massage and compresses are all worth trying. Small doses of roentgen therapy may be helpful, although the hazard of giving radiation therapy in the head and neck area is well documented. It is difficult to destroy an infectious activity in the parotid with radiation. Additional radiation will cause atrophy of the mucous membranes of the soft palate, mouth and pharynx, and the drying may be more uncomfortable than the parotitis.[8] Radiation is disappointing in that it will reduce hypersecretion but this is not a factor in chronic parotitis.

Total parotidectomy[6,15] is advised only with frequent attacks and severe, progressive disability. Parotidectomy for chronic parotitis is a much more difficult procedure than for a mixed tumor or hemangioma. The gland is indurated and inflamed. Perineural adhesions require meticulous dissection with infinite patience. The deep lobe must be removed or a salivary fistula or recurrent parotitis may occur. A secondary procedure makes seventh nerve dissection very hazardous.

One point is to be emphasized with regard to parotidectomy in infants. The mastoid process is not completely pneumatized and the stylomastoid foramen is in an unprotected and exposed position on the lateral skull surface. The nerve is only 0.5 mm in diameter and lies nearer the surface than in adults and can be easily injured.

Needle or incisional biopsy is advised for a dif-

fuse asymptomatic lesion if after complete clinical and radiographic evaluation the diagnosis is still not established. The tissue thus obtained can be used for cultures and microscopic examination.

Non-Inflammatory Tumors

The specific type of each of the following non-inflammatory tumors as determined by examination of tissue, decrees the method of management.

Hemangiomas[12,13,21]

Hemangiomas are the most common non-inflammatory tumors of the parotid in infants and children. They usually appear in the first year of life and are more frequently seen in Caucasians and in females. They may show a transient increase in size during crying or straining and, when palpated may feel soft to firm. A bluish discoloration to the skin may be evident, this sign depending on the amount of cavernous tissue component present. Most of the tumors of this order are capillary hemangiomas that are lobulated without evidence of a capsule.

Microscopically one sees solid sheets and masses of cells and anastomosing capillaries replacing parotid acinar structures leaving widely separated ducts. Silver stains for reticulum demonstrate the epithelial nature of the cells in the solid areas, distinguishing the lesion from a hemangiopericytoma,[20] as the latter occurs entirely outside of the reticulum sheet of the vessels. The two common features are (1) the formation of atypical epithelial cells in greater numbers than is required to line the vessels with a simple epithelial membrane and (2) the formation of vascular tubes with a delicate framework of reticulum fibers. The linings of the tubes have a decided tendency to anastomose. Sialograms show a distorted ductal pattern. Malignant change is extremely rare.

Many types of therapy have been reported, including surgical excision, massage, radiation, implantation of radon seeds, use of sclerosing agents, carbon dioxide snow and ligation of the external carotid artery. It is our opinion that operation should be postponed as long as possible in view of the natural history of hemangiomas elsewhere in the body. They should be given a chance to undergo spontaneous involution and regression, unless serious sequelae of growth make operation essential. Rapid growth with gradual closure of the ear canal, or encroachment toward the commissure of the mouth may precipitate the decision for parotidectomy.

Although it has been promulgated that parotid hemangiomas do not undergo spontaneous regression, complete regression without therapy was observed in one child in our series and two infants in Scarpella's[19] series. In all three instances resolution occurred within a two-year period. If operation is contemplated, we do advise waiting until the infant is at least six months of age to bypass the rapid growth and highly cellular phase of this tumor. Recurrences have been observed in infants operated upon at a younger age. There is a tendency as the patient gets older for the tumor to have a capillary and cavernous pattern with less cellularity and mitosis. This change is associated with a slower growth potential, with no significantly increased risk from greater vascularity comprising a later dissection.

As to the hazards of parotidectomy, Wolfe,[23] in a review of the literature, recorded a 4 percent mortality (two of 46 patients) and a facial nerve injury in 25 percent of cases.

Lymphangiomas[1,9]

These are uncommon in the parotid area except by extension from the cervical area. Rare cases have been presented in which the tumor was confined to the parotid gland due to sequestered intraparotid lymphati anlagen. Lymphangiomas are multioculated and composed of cystic spaces of varying size. Microscopically the cysts are composed of randomly arranged intracommunicating and dilated lymphatic channels with a flattened epithelial lining of the walls. The lesions are usually slow-growing, but rapid enlargement may follow an upper respiratory tract infection. Surgical operation is considered the treatment of choice. Radiation and radon seeds are of doubtful value.

Benign Mixed Tumors

Mixed tumors are common in adults, infrequent in children.[7] Of a total of 2,309 cases of mixed tumor reviewed by Howard,[10] only 66 (less than 3 percent) were in children. Many of these tumors are contained in a thin, delicate capsule consisting of connective tissue and remnants of compressed salivary gland tissue. In reviewing the history of cases in which there was recurrence, it was noted that in almost 80 percent of them the tumor had been broken into at the time of operation. These tumors can be round, smooth and movable or nod-

ular and fixed, and the most frequent location is the tail of the parotid gland beneath the lobule of the ear. The size varies from 4 mm to 10 cm. Histologic examination often reveals excrescences 1 mm or less in diameter which jut through the capsule. This explains the presence of multiple local recurrences. When seen in its primary manifestation the mass is usually solitary; lesions of recurrence are usually multiple. It has been noted that the recurrence rate after removal of mixed tumor is in the neighborhood of 10 or 20 percent.

The growth rate of these tumors is variable. They may remain static as a painless lump for long periods or they may rapidly increase in size. Local pressure may cause discomfort or pain. Not often if the lesion is benign is there any involvement of the seventh nerve. Ninety percent of them are in the parotid gland, about 10 percent are in the submaxillary gland and less than 1 percent in the sublingual gland. The median age of patients is 42 years. One case was reported at birth. There are no familial tendencies and no etiologic clues. X-ray has little therapeutic effect. Cut surfaces of these lesions are an homogenous grey-white. About 30 or 40 percent contain some cartilage and various mucinous material. Recurrences can appear as long as ten years later. In one case in the present series (Case 4) the growth was detected when the patient was 14 years of age. At the time of last report, nine years after resection, there was no recurrence. The treatment of a mixed tumor is complete removal of the tumor with a good margin of normal parotid gland usually by subtotal parotidectomy.

Malignant Tumors

In the case of malignant mixed tumors of the parotid area (which are uncommon in children) there is usually a history of a mass that has remained static or indolent for a long time, then has grown rapidly. These lesions are usually larger than benign tumors in the same area and they are usually fixed either to the deeper structures or to the skin. They may be partially encapsulated. Sectioned surfaces appear mushy and friable rather than tough and resilient. The malignant change can be carcinomatous or sarcomatous. Seventh nerve involvement is not common but does occur. Pain is a frequent symptom. The recurrence rate after excision is about 50 percent. Metastasis to lungs, bones, abdominal viscera and brain has been noted.

For removal, an incision giving adequate exposure is necessary in order that the tumor may be excised with good margins and without spilling the contents. Salivary fistulas occur infrequently and are usually temporary. There was one malignant mixed tumor in our series, in a six-year-old boy (Case 1).

As far as carcinomas are concerned, the most common in children, as in adults, is the muco-epidermoid carcinoma. In about one-third of the patients, the tumors persist or recur. Undifferentiated carcinoma is the second most frequent variety in children and it is the most malignant of the juvenile carcinomas in the parotid area.

Although sarcomas are rare, there were three cases in the present series, one case of malignant parotid mesenchymal tumor and one of parotid plexiform neurofibroma with sarcomatous change (Cases 2 and 3), and a rhabdomyosarcoma of the right parotid and pterygoid area (Case 5). The most common sites of origin for this tumor in the head and neck area are the orbit, nasopharynx, nose, antrum, parotid and mandible. All too frequently these tumors cannot be completely removed and require additional therapy. About 50 percent will die of their disease within one year.[14] None of the chemotherapeutic agents presently in use is curative in inoperable lesions, but Actinomycin-D and Cytoxan can cause regressions.[16]

REFERENCES

1. Bhaskar, S. N., and Lilly, G. E.: Salivary gland tumors in infancy—Report of 27 cases, Oral. Surg., Anes. and Hosp. Dental Service, 21-4:305-313, July 1963.

2. Borsanyi, S. J.: Chronic asymptomatic enlargement of the parotid glands, Am. Otol. Rhin. and Laryng., 71-4: 857-867, Dec. 1962.

3. Byars, L. T., Ackerman, L. V., and Peacock, E.: Tumors of salivary gland origin in children: A clinical pathologic appraisal of 24 cases, Ann. Surg., 146:40-51, July 1957.

4. Dargeon, H. W.: Tumors of Childhood, Salivary Glands, pp. 106-108, Copyright, 1960, Paul B. Hoeber, Inc., Medical Division, Harper and Brothers, New York.

5. Dorrance, G. M.: The treatment of chronic infections of the parotid gland, Am. J. Roentgenol., 33:803-806, June 1935.

6. Eddy, H. H., and McKenzie, G.: Surgical treatment of recurrent parotitis, Med. J. Austr., 12:715-717, 7 Nov. 1953.

7. Foote, F. W. Jr., and Frazell, E. L.: Tumors of the major salivary glands, Armed Forces Inst. Pathology, Atlas of Tumor Pathology, Section IV, Fasicle II, 1954.

8. Gerry, R. G., and Seigman, E. L.: Chronic sialadenitis and sialography, Oral. Surg., 8:453-478, 1955.

9. Hill, J. T., and Briggs, J. D.: Lymphangioma, West. J. Surg., 69: 78-81, Mar.-Apr. 1961.

10. Howard, J. M., Rawson, A. J., Koop, C. E., Horn, R. C., and Royster, H. P.: Parotid tumors in children, Surg. Gynec. Obstet., 90-3:307-319, Mar. 1950.

11. Karlan, M. S., and Snyder, W. H. Jr.: Sialadenitis and major salivary gland tumors in children, Calif. Med., 103:178-183, 1965.

12. Kauffman, S. L., and Stout, A.P.: Tumors of the major salivary glands in children, Cancer, 16-10:1317-1331, Oct. 1963.

13. Lane, S., and Schwarz, A. W.: Infantile hemangio-endothelioma of the parotid gland, Am. J. Surg., 96:784-786, Dec. 1958.

14. Mason, J. K., and Soule, E. H.: Embryonal rhabdomyosarcoma of the head and neck: Report on 88 cases, Am. J. Surg., 110:585-591, 1965.

15. Pearson, R. S. B.: Recurrent swellings of the parotid gland, Arch. Dis. in Children, 10:363-376, 1935.

16. Pinkel, D., Pickren, J.: Rhabdomyosarcoma in children, JAMA, 175:293-298, 1961.

17. Reiquam, C. W.: Salivary gland tumors in children, Arch. Surg., 86-2:313-317, Feb. 1963.

18. Rush, B. F. Jr., Chambers, R. G., and Ravitch, M. M.: Cancer of the head and neck in children, Surgery, 53-2:270-284, Feb. 1963.

19. Scarpella, J. V., Dykes, E. R., and Anderson, R.: Hemangioma of the parotid gland, Plast. & Reconstruct. Surg., 36-1:39-47, July 1965.

20. Stout, A. P.: Hemangio-endothelioma: A tumor of blood vessels featuring vascular endothelial cells, Ann. Surg., 118:445-464, Sept. 1943.

21. Wawro, N. W., Fredrickson, R. W., and Tennaunt, R.: Hemangioma of the parotid gland in the newborn and in infancy, Cancer, 8:595-600, May-June 1955.

22. White, I. L.: Recurrent parotitis with sialangiectasis, Calif. Med., 98:90-93, Feb. 1963.

23. Wolfe, J. J.: Congenital hemangioma of the parotid gland, Plast. and Reconstruct. Surg., 29-6:692-697, June 1962.

ANTICOAGULANTS

"I think the two points we don't emphasize about anticoagulants are these: first, the socio-economic factor. The biggest contraindication to anticoagulants is the fact that the patient is not reliable to get a prothrombin time; the nearest laboratory is not reliable; and there's no one in the family who will make sure that they take the right dose. The patient who is not reliable is absolutely precluded from anticoagulants. Then another point on the other side — very helpful, I think — is what I call the sum of incomplete indications. You frequently see a person with amaurosis fugax who doesn't have enough of that in itself to have an indication of anticoagulants. But if he has a little bit of angina and a little bit of intermittent claudication and may have had a previous bout of myocardial insufficiency, you call up the cardiologist, 'Do you think this angina is bad enough to anticoagulate?' No. And you call up the peripheral vascular surgeon, 'Is his intermittent claudication enough to anticoagulate?' No. But by the time you have two or three or four of these episodes and know that the man does have widespread vascular disease, I think you may consider the incomplete indications in favor of anticoagulation.

"The points I'm emphasizing on anticoagulants: The commonest contraindication to anticoagulants is the socio-economic factor; the patient cannot afford to have the tests; the laboratory is not reliable; people are not dependable. In my experience, the commonest indication is the sum of incomplete indications."

—J. Lawton Smith, M.D.

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Clinical Chemistry

A Retrospective Look at Routine Screening

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RECENTLY THERE HAS BEEN a surge of interest in automated clinical chemistry and of routine blood chemistry screening tests. Chemistry panels are being advocated for routine hospital admission studies, periodic health examinations, routine diagnostic surveys, detection of pre-disease, chemical fingerprinting and predictive medicine.

Enthusiasm has been expressed for these screening tests since costs seem reasonable and the incidence of abnormal findings seems to be great. Cost reductions are realized in doing large numbers of tests with multi-channel analysis. However, fewer test channels might well be done more cheaply. The extra cost for more test channels may not be justified if these additional studies do not provide information significantly useful to the particular patient.

Good medicine should not relate only to cost but primarily to good patient care. For example, if a routine admission study included a blood glucose and urea so that occult diabetes mellitus or renal insufficiency might be detected, it may not be pertinent to do routinely determinations of, say, sodium, chloride, carbon dioxide content and acid phosphatase, just because they can be done at little extra cost. It is already obvious from general surveys that there is no practical value in doing a serum acid phosphatase determination in a health evaluation screening study, and sodium, potassium, chloride and carbon dioxide content may also be of no value.

Literature and personal communications are reviewed in this paper in an attempt to determine if routine chemistry screening was in the interests of the best practice of medicine. It was apparent in the beginning of this study that optimistic reports on the value of chemistry screening did not give enough consideration to the problems of defining the meaning of abnormal and unsolicited significant abnormal findings. Therefore, this review, which advocates a conservative view toward unsolicited routine chemical screening programs, is presented.

Incidence of Abnormal Findings

The incidence of abnormal findings in any study is influenced by the criteria for normal values and by how an individual report is judged to be abnormal. This alone leads to variations in estimating the incidence of abnormal findings in any survey of data.

The AMA Exhibit Laboratory in 1962 reported on experiences with blood chemistry as shown in Table 1.[1] A breakdown of the distribution of abnormal values is seen in Table 2. One might challenge whether borderline values, such as those for uric acid, should have been included as abnormal findings. Table 3, derived from Young's data, illustrates the possible variations in the interpretation of laboratory data.[2] The incidence of abnormal findings in Young's presentation is modified by considering the day-to-day technical variability commonly observed with these assays. The percent of abnormal findings after modifications is notably different, and this is most pronounced for the electrolytes.

The dilemma of what is abnormal is further illustrated in Table 4, which is based upon information in reports[1,3,4] of AMA Exhibit Laboratory Surveys. Cholesterol assays in 1966 had some

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recognizable technical problems to possibly explain the change in the incidence of abnormal findings. The decreased incidence in abnormal findings for uric acid in 1965 and 1966 and for glucose in 1966 is most striking, and is not explained. The significance of these abnormal findings is unknown.

Plans are being made to follow up the significance of abnormals from the 1966 AMA survey. The change in incidence of abnormal findings might suggest that the physicians have been successfully treating the chemical abnormalities. This seems unlikely in that there was no striking change between the 1962 and 1965 surveys for glucose and cholesterol. The 1965 high incidence of blood

TABLE 1.—*Findings at AMA Exhibit Laboratory, 1962*[1]

Blood Chemistry	*Number Abnormal*	*Percent of Those Tested*
Elevated serum glucose	378	21
Low serum glucose	1	.06
Elevated serum cholesterol	533	30
Low serum cholesterol	1	.06
Elevated uric acid	632	36
Elevated transaminase	56	3.1
Low serum protein	9	.5
Low serum albumin	10	.5
Elevated alkaline phosphatase	24	1.3
Elevated acid phosphatase	0	0
Elevated serum urea nitrogen (18 or more)	319	18

1,963 chemical abnormalities found in 1,771 physicians. Approximately two-thirds of physicians showed at least one abnormality.

TABLE 2.—*Range of Abnormalities in Blood Chemistry*[1] *at AMA Exhibit Laboratory, 1962*

	Borderline	*Moderate*	*Severe*	*Total*	*Percent*
GLUCOSE mg/100 ml	(120-150)	(151-200)	>200		
Number of physicians	260	95	23	378	21
CHOLESTEROL mg/100 ml	(275-325)	(326-400)	>400		
Number of physicians	404	89	40	533	30
URIC ACID mg/100 ml	(6.5-7.5)	(7.6-8.5)	> 8.5		
Number of physicians	309	194	129	632	36

TABLE 3.—*Interpretative Variation in Incidence of Abnormal Findings*[2]

Test	*Number of Patients*				*Corrected**			
	Low	*Norm*	*High*	*Total*	*Abnormals*	*Percent of Total*	*Abnormals*	*Percent of Total*
Glucose	34	318	37	389	71	18	30	7.5
Urea N	12	320	58	390	70	18	25	6.4
Creatinine	..	364	23	387	23	6	10	3.7
Sodium	85	309	..	394	85	22	6	1.5
Potassium	78	315	..	393	78	20	14	3.6

*Corrected abnormals are estimated by comparing reports with the normal range utilizing a usual value for day-to-day technical variability (±2 SD) to determine abnormality with 95 percent certainty. A result is significantly abnormal if outside the limits of normal range ± the technical variability expressed as ±2 SD.

TABLE 4.—*AMA Exhibit Laboratory Surveys*[1,3,4] *1961 to 1966 Comparisons*

Serum	*Incidence of Abnormal Findings*		
	1966	*1965*	*1962**
Urea Nitrogen	18%	59.0%	18%
Uric Acid	10%	9.3%	36%
Glucose	4%	17.1%	21%
Cholesterol	3% (18% unsatisfactory)	34.0%	30%
Ca, LDH, SGO-T	1%	—	—
T-3	<1%	—	—
Phosphorus	Normal in practically all persons tested	—	—
Protein; albumin	Normal in practically all persons tested	—	0.5%

*Results for 1961 to 1964 surveys were essentially same.

TABLE 5.—*Distribution of Abnormal Values in AMA Exhibit Surveys*[1,4]

	1962			1965		
	Total Percent Abnormal	*Abnormal Range*	*Number of Patients*	*Abnormal Range*	*Number of Patients*	*Total Percent Abnormal*
Glucose	21	(120-150)	260	(120-159)	343	
		(151-200)	95	(160-200)	36	17.1
		(>200)	19	(>200)	23	
Cholesterol	30	(275-325)	404	(250-300)	553	
		(326-400)	89	(300-350)	160	34
		(>400)	40	(>350)	24	
Uric Acid	*36*	(6.5-7.5)	309	(7.0-8.9)	*211*	
		(7.6-8.5)	194			17.1
		(>8.5)	129	9.0 or >	7	
Urea N	*18*	(>18)	319	(18-25)	970	
				(26-40)	386	*59*
				41 or >	2	

urea nitrogen (BUN) also represents an unexplainable problem of defining normal values in a survey. The distribution of values in comparing 1962 and 1965 surveys does not explain the urea findings in 1965 as noted in Table 5.

The published findings of Thiers[5] are presented in Table 6 and are compared with the 1962 AMA Survey. It is striking that the ambulatory physicians attending a medical meeting are more chemically "sick"—that is, abnormal—than patients being admitted to a general hospital. It is also of interest that the outpatients in Toronto are more "sick" than the inpatients in North Carolina, as illustrated by the incidence of abnormal patients in Table 7. Obviously, then, the designation of an abnormal finding is still clouded by variable criteria and is a subject worthy of additional investigation.

Significant Abnormal Unsolicited Findings

If the problem of determining abnormality is not considered of sufficient moment to some, there is little doubt as to the complexity of the problem when one attempts to determine whether a laboratory finding is necessary or significant for the patient. There have been attempts to evaluate the significance of abnormal findings when these findings are obtained in an unsolicited or routine chemistry screening program. In Thiers' study,[5] 5 percent of inpatients had significant diagnostic abnormal findings, and in Young's study,[2] 2.3 percent of patients had findings which were considered significant as noted in Table 7. Even though both studies included a chemistry panel of ten to eleven tests, about 70 percent of the so-called significant abnormal findings were due to glucose and urea determinations.

In Thiers' study,[5] which initially publicized the application of multi-channel testing, the large multi-channel machine did nine of the tests while a dual channel machine did the glucose and urea determinations. Young's study[2] was further complicated by the fact that only 21 percent of all the patients, who were thought to be significantly abnormal for follow-up, were considered significant after follow-up. Therefore, at least four out of five possibly significant abnormals led to studies which proved the findings to be of no significance and thereby represents a kind of false alarm or

TABLE 6.—*Incidence of Abnormal Tests and Patients Demonstrate that "Well" Physicians are more Abnormal than "Sick" Patients*

Source	*Total Tests*	*Total Patients*	*Total Abnormal Chemistry*	
			Tests	*Patients*
AMA 1962 Survey[1]	17,771	1,771	1,963	*1,181**
Panel: 10 Chemical determinations	Percent of Totals		11	*67*
Duke U.[5]	17,391	1,581	1,080	600
Panel: 11 Chemical determinations	Percent of Totals		6.4	36
Community Hospital[5]	7,062	642	205	154
Panel: 11 Chemical determinations	Percent of Totals		2.9	25
VA Hospital[5]	6,853	623	330	223
Panel: 11 Chemical determinations	Percent of Totals		4.9	36

*These values include all laboratory tests done which include predominantly chemistry studies.

wasted effort working up the patient. Table 8 shows the detailed analysis of outpatient findings from Young's study.[2]

Most clinical pathologists engage in a great deal of discussion with house staff as to whether a test should or should not have been done, and whether or not a result, abnormal or normal, was of significance in providing patient care. A great variation of opinion is most often expressed. This directs one's attention to the fact that significant abnormalities were defined in the Thiers' study[5] by one physician and the pathologist at the VA Hospital. In the Skeggs' study,[6] the designation of unexpected significant abnormal findings was estimated by comparing the abnormal findings with the principal diagnosis obtained by a review of the patient's clinical records.

It is of interest that although there were 149 unexpected abnormal findings noted in Thiers' data[5] (Table 9), only 54 were deemed significant. The uncertainty of data expressivity is evident in that 23 of 28 hyperuricemic findings were considered medically significant, but only four cases of gout were discovered; whereas 16 of 31 abnormal

TABLE 7.—*Significance of Abnormal Unsolicited (Unexpected) Findings*

Source	*Total Patients*	*Unsolicited Abnormals*	*No. of Significant Unsolicited Abnormals*	*Glucose Diabetes*	*Urea Renal Disease*	*Other*	*Comment*
Thiers[5] VA Hospital Inpts. Panel: 11 Chemistries	623	105	31	15	7	9	includes uric acid and cholesterol (1 myeloma)
	% of totals	17	5	2.4	1.1	1.4	
Young[2] Toronto General Outpatients Panel: 10 Chemistries	398	211	9	4	3	2	does not incl. uric acid and cholesterol (1 hyperparath?) (1 asthma)
	% of totals	53	2.3	1.0	0.8	0.5	

			Analysis of Abnormals			
Total Patients	*Abnormals*	*Expected Confirm Dx.*	*Insufficient Significance no follow-up*	*Biochem. dx. uric acid cholesterol (antibodies)*	*Significant after follow-up*	*Significant for follow-up*
398	211	65	81	23	42	9
% of totals	53	16	20	6	11	2.3

TABLE 8.—*Distribution of Findings from Clinic Outpatient Study*[2]

With usual routine UA, Hgb. and blood film scan, and an extra panel of tests including Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, CO_2 content, Phosphorus, Uric Acid, Calcium (and Sedimentation Rate, Serologic Test for Syphilis, Blood Group and Typing)

Percent	*Number of Cases*	
	398	Total studied
26.0	103	New information normal
18.0	72	New information normal (after at least one value reported was rejected as a lab error or artifact)
16.0	65	Abnormal values reported confirmed the dx.
20.0	81	Abnormal values reported insufficiently significant to require follow-up
5.8	23	Assigned biochem. dx. not needing follow-up (hyperuricemia, hypercholesterolemia, irregular antibody formation)
10.6	42	Abnormal finding seemed of sufficient significance to require follow-up
1.00%	*4*	New information was erroneous
1.00%	*4*	Diabetes mellitus (additional dx.)
0.50%	*2*	Uremia (additional dx.)
0.25%	*1*	Polycystic disease rather than splenomegaly
0.25%	*1*	Asthma and chronic bronchitis substitute for dx. arteriosclerosis
0.25%	*1*	Not followed up
0.25%	*1*	Strongly suspected of hyperparathyroidism
7.30%	*29*	Significance obscure
10.60%	*42*	

TABLE 9.—*Incidence of Unexpected Abnormal Test Results*[5]

	Total	*Medically Significant*
Glucose	31	16
Urea	7	4
Na	10	0
K	25	1
Cl	2	0
CO_2	6	1
Ca	6	1
Phosphorus	10	2
Protein	15	2
Albumin	9	4
Uric Acid	28	23
Totals	149	54

Note: The large number of unexpected abnormal findings might lead to useless investigations.

TABLE 10.—*OUTPATIENT SURVEY—10 Channels: Serum Sodium, Potassium, Chloride, CO_2 Content, Urea, Glucose Calcium, Protein, Albumin, Phosphatase, Bilirubin, Transaminase* (SGOT)[6]

97 out of 480 patients (20 percent) were abnormal
83 of 97 had medical records examined
66 of the 83 patients revealed unexpected abnormal finding based upon the principle diagnosis
- 15 patients (glucose>150) possible diabetes
- 11 patients mild degree of N retention (urea>20)
- 41 patients with impaired liver function (abnormal bilirubin, and/or alk. phosphatase, and/or SGOT) (Most of patients had diagnoses of hypertension, alcoholism, or schizophrenia; drugs?)
- 5 patients (protein>8.9) elevated serum protein (significance was unexplained)

No follow-up studies confirming significance of abnormal findings are reported

glucose findings were considered medically significant and eventuated in the detection of 15 cases of diabetes mellitus. It is, therefore, apparent from the point of view of clinico-pathologic correlation, that an abnormal glucose finding is more likely to be of clinical significance than a high uric acid finding. Metabolic alterations having no evident clinico-pathologic correlation are really of doubtful or unknown medical significance.

The findings in Skeggs' study[6] reveal the Cleveland outpatients to be chemically healthier (fewer abnormal findings) than the physicians attending the AMA meeting. Table 10 shows that except for the large number of patients with apparently impaired liver function, the major number of significant findings again seems related to glucose and urea determinations.

It is of interest that most of the patients with impaired liver function had histories of hypertension or alcoholism or psychosis, and no mention was made of whether the patients were taking drugs that might possibly explain the chemistry findings. If due to drugs abnormality of liver function tests might represent a transient pharmaceutical chemical event rather than any significant tissue alteration. It is also most disconcerting to notice that follow-up studies to confirm or evaluate the possible significance of these abnormal findings were not done in this study. For example, the significance of urea retention was not evaluated by doing renal clearance studies or creatinine assays, or even a concentration test for renal function in order to ascertain whether it was due to renal disease.

The findings in Table 11 are from an outpatient serum calcium survey.[7] Six hundred out of almost 12,000 patients were classified as abnormal. Of these, only 21 were classifiable as significantly abnormal after repeat assays and additional studies led to a final diagnosis. It should be noted that a parathyroid adenoma was detected in fewer than one patient in 1,000. Review of tables in the article seems to indicate that the diagnosis was suggested in most instances from the clinical findings. Autopsy experiences have revealed up to six adenomas in 76 consecutive autopsies. Therefore, since parathyroid adenomata may be more common than evidenced chemically, when does hypercalcemia occur? When is it important to diagnose hypercalcemia? When again should this population be resurveyed for abnormal serum calcium levels? Studies are definitely needed to determine how often a survey should be repeated.

Other Comments

Chemistry panels and screening examinations may vary, depending upon their purpose. After introducing a 12-channel automated analysis system which included serum electrolytes, the automation manufacturer developed an outpatient diagnostic 12-channel machine which substitutes assays of presumably greater importance than the electrolytes of the original panel. It does seem that the instrument maker or the chemist should not be in the responsible position of deciding on the constituents of chemistry panels or screening. This should be achieved by physicians who are knowledgeable as to the medical needs of patients as well as the financial and technical aspects of the problem.

If present or future medical practice must consider routine chemistry admission studies, these

TABLE 11.—*Routine Serum Calcium Survey Outpatients (after Boonstra)*[7]

	Abnormal Patients 8.8 to 10.4 (95)	*Significant Abnormal**	*Other***
I. Total tests (patients):			
11,991	600	21	539
% of totals	5%	0.21%	4.8%
% of abnormals	—	3.80%	96.0%

*Repeat assays, additional studies, final dx. established.
**After repeat assays: includes technical error, previously established diagnoses, no definite diagnosis.

Total	*Primary hyper-parathyroidism*	*Hypo-parathyroidism*	*Milk alkali syndrome*	*Multiple myeloma*	*Malignancy with bone metastases*	*Hyper-aminoses Vit.-D*
II. Evaluation of patients with the significant abnormal findings:						
11,991	10	3	2	1	5	2
% of total	0.083% (9 adenomas)	0.025%	0.025%	0.008%	0.045%	0.016%

could consist of serum glucose and urea, or creatinine. The development of multi-channel or automated analysis should consider elective pre-operative chemistry studies on major surgical patients. This might include sodium, potassium, chloride, bicarbonate, glucose, urea, protein, transaminase (SGO-T) and bilirubin. An elective diagnostic chemistry survey for patients with medical diagnostic problems could also include serum calcium, protein-bound iodine, alkaline phosphatase, uric acid, and cholesterol, as well as the constituents of the pre-operative chemistry studies. A renal function panel could include serum urea nitrogen, creatinine, sodium, potassium, chloride, and carbon dioxide content. A liver function panel could consist of serum total and direct bilirubin, alkaline phosphatase, transaminase, and prothrombin time. These represent only some of the grouping that could be considered in the best interest of good laboratory medicine rather than in terms of instrument or instrument manufacturers' convenience. An appropriate chemistry panel requisitioned by a physician for a particular patient rather than the routine indiscriminate application of the machine to a patient's blood specimen, will be in the best interests of progressive and good medicine.

In a most recent article Rardin[8] reported experiences with laboratory profile screening in the physician's office. Review of this paper reveals that out of 18,300 tests done, there were 257 (1.4 percent) in which results were reported as medically significant. Medical significance was defined as data which confirmed a known disease or led to a new or more complete diagnosis. Based upon usual experiences, it is probable that unexpected significant abnormal findings are fewer than expected findings and, therefore, only represent about 0.3 to 0.15 percent of the tests done. No attempt was made in the paper to indicate how many patients rather than tests might be involved with unexpected significant findings revealed by the survey.

In conclusion, the following reflections are offered. They are based upon the review of chemistry screening surveys presented in this paper and the ill-defined criteria for normal, abnormal and significantly abnormal findings.

- The need for further efforts to define what is significantly abnormal is most evident. This is exemplified by the fact that ambulatory physicians attending medical meetings are "more sick" (more abnormal) than the patients they have been admitting for hospitalization or seeing as outpatients attending a general hospital clinic.

- Significant unsolicited abnormal findings have been reported in from 2 to 5 percent of patients studied. Approximately 70 percent of these so-called significant abnormal unsolicited chemistry findings are related to blood glucose and urea. These determinations have been recommended for many years by some physicians as part of the routine medical examination. Nine to ten additional chemistry tests led to detecting only approximately 30 percent of the apparently significant unsolicited findings, and this represented less than 1 or 2 percent of patients studied.

- Unsolicited *abnormal* chemistry findings lead to a great deal of additional studies. Approximately 80 percent of the time, these lead to conclusions having no clinical significance for the patient.

• Even when chemistry studies are not done routinely but are ordered as clinically indicated, their significance is difficult to evaluate. This has always been a problem. Interns and residents are often accused of ordering too much laboratory work as compared with the sophisticated attending physician. The general consensus in the field of laboratory medicine used to be that we obtain plenty of data, and that the major problem is the interpretation of findings. We should avoid exaggerating this problem by introducing overwhelming amounts of useless information.

• Little information, if any, is available as to how often the chemistry screening examination should be repeated for a given individual, or for a specific population of patients.

• We should be reserved and careful in the application of laboratory screening methods to avoid what might be the fostering of "decerebrate"[9] rather than good laboratory medicine.

• Predictive medicine and diagnostic automated chemistry screening panels seem to be an exciting challenge in the field of clinical pathology. These concepts deserve and require a great deal more experience and research before uniform measures should become generally acceptable to physicians, patients and politicians.

ADDENDUM: Some interesting comments confirming some of the impressions referred to in this paper are evident in the Editorial entitled "Who's for Screening?" in the 30 September 1967 issue of *Lancet,* page 706.

REFERENCES

1. Peery, T. M.: The role of the laboratory in health evaluation, Interim Report No. 77, from the 1964 Technicon International Symposium, New York, New York.
2. Young, D. M., and Drake, T. G. H.: Unsolicited laboratory information, presented to the College of American Pathologists, Chicago, 18 Oct. 1965.
3. Martens, V. E.: AMA Exhibit Laboratory 1966, The Bulletin of Pathology, Sept. 1966, p. 221.
4. Martens, V. E., Peery, T. M., and Montgomery, L. G.: Clinical pathology tests in health evaluation, 1966, p. 14. A brochure prepared for the Exhibit Laboratory, presented at the Annual Meeting of the American Medical Association, Chicago, June 26 to 30, 1966.
5. Bryan, D. J., Wearne, J. L., Vian, A., Musser, A. W., Schoonmaker, F. W., and Thiers, R. E.: Profile of admission chemical data by multi-channel automation: An evaluative experiment, Clim. Chem., 12:137-143, 1966.
6. Skeggs, L. T.: Outpatient screening experiment, personal communication of mimeographed text, 5/18/65.
7. Boonstra, C. E., and Jackson, C. E.: The clinical value of routine serum calcium analyses, Ann. Intern. Med., 57:963-969, 1962.
8. Rardin, Thomas E.: Laboratory profile screening in the family physician's office, JAMA, 198:1253-1256, 1966.
9. Editorial: Routine laboratory tests, New Eng. J. Med., 275:56, 1966.

CONFIRMING A DEBATABLE LUNG CANCER

Cytology and other diagnostic approaches to confirming a debatable lung cancer . . .

"There are many differential diagnostic points in cytology of bronchogenic carcinoma. I would like to bring to your attention one lesion which is not a cancer, but is cancer-related and with which you may in due course of events become increasingly familiar. Certain drugs used in the treatment of cancer may produce significant lesions in otherwise non-affected tissues. One such drug which produces extensive pulmonary lesions is busulfan, known commercially as Myleran, a drug used for the treatment of chronic myelogenous leukemia. Patients who receive this drug may develop significant abnormalities of their pulmonary fields. What is particularly important is that, in the fibrotic portions of the lung, the bronchioles and alveolae contained therein are often lined by very bizarre giant cells as a result of drug effect. Such cells may, of course, appear in the sputum as well, thus being mistaken for lung cancer."

—LEOPOLD G. KOSS, M.D., New York City
Audio-Digest *General Practice,* Vol. 16, No. 12

The Battered Child Syndrome

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■ *This is a report of socio-medical aspects of 23 episodes of physical abuse among 21 children, and findings include one death, a predominant age below two years, no unusual race or sex distribution, a high incidence of head trauma, skin lesions and bone changes, with a common history of previous abuse in the patient and siblings. Intact families had few children in the house. Parents were usually young, had a high incidence of illegitimate births, mental disease and previous criminal records. Abuse was often inflicted by a close relative, usually the mother.*

Incidence and severity of physical abuse in California and participation in therapy are discussed.

EPIDEMIOLOGIC PROJECTIONS by Gil[1] suggested that in 1967 California would lead the nation in incidence of physically-abused children. His discovery of 1,300 cases in California for that year would indicate that this socio-medical disease reached epidemic proportions.[2]

The early literature with its emphasis on clinical manifestations provided clinicians with important diagnostic information,[3-7] but beyond diagnosis lies therapy and prevention of future episodes. Significant accomplishments in these areas are linked to a more thorough understanding of the socio-medical aspects of the battered child syndrome.

It is the purpose of this report to focus on these findings and their severity, based on our experience in San Francisco.

Material

This study of 23 separate incidents involves 21 physically-abused children from 18 families who were seen between May 1966 and June 1967 as part of a collaborative program between the San Francisco General Hospital, Division of Social Services, and Juvenile Court of the City and County of San Francisco.

Ten families were receiving public assistance, six had incomes between $4,600 and $10,800 a year, and in two instances the income was unknown. While the study group included a predominance of families in poverty, six had incomes that were commensurate with middle class families in the community.

Results

Most of the abused children were quite young. The majority were less than three years of age when the physical abuse was brought to the attention of the community, but this did not preclude abuse at a younger age. In the group were 15 Caucasians and six Negroes. Distribution of the sexes was about equal (Table 1).

Generally, the families were small; the majority had one or two children in the home. Of nine children born out of wedlock six remained illegitimate and three were legitimized by marriage. Fourteen

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families were intact, with a father or father figure in the home. Most of the parents were between the ages of 16 and 25 years, with a small age differential between parents; and, with only one exception, the father was always older than the mother. Mental disease (chronic brain syndrome, paranoid schizophrenia, neurotic tendencies and extreme immaturity) was found in one or both adults in nine families. In 12 families, one or both adults had previous criminal records. Marital discord, financial stress, child neglect, impulsive behavior, reversal role of parents, strict disciplinary action, parents from similar backgrounds, sexual promiscuity and provoked incidents by children were present sporadically in varying degrees (Table 1).

Head trauma was the most common finding (15 without obvious central nervous system damage, two subdural hematomas, one concussion, one skull fracture). Ecchymosis, abrasions or scars were present in 13, lacerations in two, and burns in two, and bone changes in nine of 18 children surveyed; and one had cardiac damage. Of the recorded weights in 18 children, three were under the 3 percentile. From hematocrit levels in 16 cases, anemia was noted in four. One two-year-old Indian female was brutally beaten to death. Noted at autopsy were a subdural hematoma, traumatic fracture of first lumbar vertebrae with epidural hemorrhage of spinal canal, traumatic laceration of liver, retro- and intra-peritoneal hemorrhage, contusions, lacerations, acute pulmonary edema, congestion and hemorrhage. In all cases, the patient was proven or surmised to have been abused by a close family member, often the mother. The person who perpetrated the abuse usually brought the child to the hospital or a private physician for medical care (Table 2).

In most cases there was some evidence of previous physical abuse. In six of ten families with more than one child, other children were physically abused (Table 2).

TABLE 1.—*Psycho-social characteristics of abused children and their families*

	Children		
Age of children (yr.)	*Male*	*Female*	*Total*
<2			9
2-3			5
3-5			4
>5			3
Race:			
Caucasian	8	7	15
Negro	3	3	6
No. in home			
1			8
2			3
3			4
4			3
Children born out of wedlock			9
Remained illegitimate			6
Legitimized by marriage			3

PARENTS:	Mother	Father Father Figure
In home	18	14
Age: (yr.)		
16-20	6	5
21-25	6	2
26-30	3	3
>30	3	4
Mental Disease Present	7	5
Previous criminal record	7	11

Discussion

While recent mortality figures are not available, our experience suggests that child battery may be one of the more common causes of death among children in California. In the last six months of 1967 the mortality rate among newly identified cases in our program increased to 12 percent.[8] It has been speculated that mortality from physical abuse may be more common than death from leukemia, cystic fibrosis or muscular dystrophy.[9] Potential and real damage in this condition is clearly illustrated in this series; beatings around the head were commonplace. Additionally, many of the children had significant bone trauma and two had internal injuries. Some children were assaulted on numerous occasions and siblings also suffered attacks. The severity is compounded by the repetitive exacerbations of this disease.[4,10,11]

An elaboration of socio-medical findings provides an indispensable insight into appropriate

TABLE 2.—*Characteristics related to child battery*

Clinical findings:	*No.*	
Head trauma	19	
Skin lesions	17	
Bone pathology	9	
Death	1	
Perpetrator of abuse:	*Proven*	*Suspect*
Mother	8	6
Father	5	2
Mother and father	—	1
Grandmother	1	—
Perpetrator who takes patient for care:		
Mother	6	
Father	4	
Previous abuse		
Study patients	15	
Siblings	6	

therapy. Several common characteristics have emerged from our study. At the time of diagnosis, the family unit usually consisted of a young mother, a slightly older father or father figure, and one or two children. The seeming tendency toward small families may not be characteristic, since siblings in six families were in voluntary or court-ordered placement. Illegitimate births were common among abused children and occasionally led to forced marriage. While families were intact, they rarely functioned well as cohesive units, and harmony was disrupted by a multitude of stresses, including mental disease, criminality, impulsive behavior, marital discord, promiscuity and financial insecurity.

Skin lesions were the only findings in most patients. However trauma to multiple areas—head, skin, bones, and/or internal organs—was quite common. Short stature and anemia, findings noted by other investigators,[12] were observed in a few patients.

Current emphasis in management is linked to mandatory reporting laws in all the States, District of Columbia, Guam and the Virgin Islands. Unfortunately, many physicians have withdrawn from cases after fulfilling the legal obligation of reporting. It seems inappropriate to divorce diagnosis from therapy—the former handled principally by physicians and the latter by jurists. No one has willfully excluded physicians from therapeutic schemes. Quite the contrary, jurists and others welcome physician participation in social planning.[8] In court, the physician can strongly influence the ultimate decision through written opinions and testimony. Judges, referees, and probation officers view the medical profession as an untapped resource for referral of battered children.[8] It seems appropriate to accept this challenge particularly in view of current incidence and mortality figures. The socio-medical data presented here and elsewhere[5,13-18] provide a basic understanding upon which one can build therapeutic programs.

REFERENCES

1. Gil, D. G.: Nationwide Epidemiologic Study of Child Abuse, Paper presented at the National Conference of Social Welfare, Chicago, Ill., June 1966.

2. Brimlow, M.: Unpublished data, 1967.

3. Caffey, J.: Multiple fractures in the long bones of infants suffering from chronic subdural hematoma, Amer. J. Roentgen., 56:163-173, 1946.

4. Gwinn, J. L., Lewin, K. W., and Peterson, H. G., Jr.: Roentgenographic manifestations of unsuspected trauma in infancy, JAMA, 176:926-929, 1961.

5. Kempe, C. H., Silverman, F. N., Steele, B. F., Droegemueller, W., and Silver, H. K.: The battered-child syndrome, JAMA, 181:17-24, 1962.

6. Silverman, F. N.: The roentgen manifestations of unrecognized skeletal trauma in infants, Amer. J. Roentgen., 69:413-427, 1953.

7. Woolley, P. V., Jr., and Evans, W. A., Jr.: Significance of skeletal lesions in infants resembling those of traumatic origin, JAMA, 158:539-543, 1955.

8. Sussman, S. J.: Unpublished data, 1967.

9. Fontana, V. J.: The Maltreated Child; The Maltreatment Syndrome in Children, published by Charles C Thomas, Springfield, Ill., 1964.

10. Boardman, H. E.: A project to rescue children from inflicted injuries, Social Work, 7:43, 1962.

11. Elmer, E.: Identification of abused children, Children, 10:180-184, 1963.

12. McHenry, T., Girdany, B. R., and Elmer E.: Unsuspected trauma with multiple skeletal injuries during infancy and childhood, Pediatrics, 31:903-908, 1963.

13. Cohen, M. I., Raphling, D. L., and Green, P. E.: Psychologic aspects of the maltreatment syndrome of childhood, J. Pediat., 69:279-284, 1966.

14. Elmer, E.: Children in Jeopardy, University of Pittsburgh Press, Pittsburgh, Pennsylvania, 1967.

15. Morris, M. G., Gould, R. W., and Matthews, P. J.: Toward prevention of child abuse, Children, 11:55-60, 1964.

16. Nomura, F. M.: The battered child "Syndrome," A Review, Hawaii Med. J., 25:387-394, 1966.

17. Nurse, S. M.: Familial patterns of parents who abuse their children, Smith College Studies in Social Work, 35:11, 1964.

18. Zalba, S. R.: The abused child. II. A typology for classification and treatment, Social Work, Jan. 1967.

A Current Review of Psoriasis

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AN ENGLISH PHYSICIAN, Robert Willan, is credited with the first accurate clinical description of psoriasis, in 1808.[121] Before that time, this common cutaneous illness was confused with leprosy, syphilis, tuberculosis or other skin diseases. The differential diagnosis of leprosy in biblical times (Leviticus, Chapter 13, King James version) leads one to the speculation that many of the "unclean" were in reality psoriatic.

Many advances have been made over the last 10 to 15 years in the study of this protean cutaneous illness. Significant studies have increased our understanding of the anatomy and chemistry of the psoriatic lesion, but we still have no explanation for the exact pathogenesis of psoriasis. It would now appear that the disease is genetically transmitted, but its capricious course, characterized by exacerbations and remissions, continues to confront experienced investigators.

Incidence and Genetics

Estimates of the frequency of psoriasis among the population at large have varied from 2.5 to 8 percent.[84] Most of these studies were carried out on hospital in-patients or out-patients, which makes it difficult to determine the actual prevalence of the disease in the general population.

Farber and Peterson approximated the incidence of psoriasis to be 1 or 2 percent in the population of the United States; if all mild cases were included, this might be as high as 3 to 4 percent.[47] Forssman found a frequency of 1.4 percent among a group of psychiatric outpatients in Sweden.[52] Based on a personal examination of a large population group, also in Sweden, Hellgren found an incidence of 3 percent; and, in a similar study, Lomholt[64,84] found the incidence in the Faroe Islands to be 2.8 percent. It is evident that despite the difficulty in obtaining accurate statistics, psoriasis is a common worldwide disease with an incidence between 1 and 3 percent.

Psoriasis is uncommon or rare in some populations, possibly due to genetic factors. Very few psoriatic persons were discovered in a survey conducted at a Nigerian teaching hospital, and in Eskimos the disease is reported to be rare.[46,122] It is also rarely seen in North or South American Indians.[28,77]

Numerous studies in the past have shown a variable sex incidence, but the current consensus is that the occurrence of psoriasis is equal in males and females.[84,127] Steinberg and coworkers noted the age of onset and mean age of affected males and females differed; clinical disease developed in females at an earlier age, and the mean age of statistically studied groups of females with psoriasis was three to four years less than that of comparable male groups.[127] Lomholt's findings were similar.[84] Farber and Carlsen reported that, in their series of 1,000 cases, 32 percent of females had lesions of psoriasis before the age of 15 years; only 20 percent of males were affected before this age.[44]

Observations of the familial incidence of psoriasis in large kindreds in Utah and North Carolina revealed a simple autosomal dominance with incomplete penetrance. In the North Carolina study, penetrance was reduced to approximately 60 percent, although penetrance in most other reported series is considerably lower.[1,142] Whether this simple dominant pattern of inheritance applies to all families afflicted with psoriasis is a moot point; several authors have suggested that mutation occurs at more than one chromosome locus or that multiple alleles appear at the same chromosome locus to produce clinical disease.[1,21,127] Steinberg and coworkers postulated a double recessive in-

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heritance.[127] Lomholt concluded from his study that inheritance could be either dominant with incomplete penetrance or double recessive. Some investigators still postulate sex linkage, but if this exists it must not be the only genetic pathway.[21]

Lomholt made the following calculations based on his study in the Faroe Islands: If two parents without psoriasis have a child with psoriasis, there is a 17 percent chance that subsequent children will have the disease; if one parent has psoriasis, there is a 25 percent chance that subsequent children will have psoriasis, and this figure is increased to 31 percent if one child is already affected; a mating of two people who have psoriasis has a 60 to 75 percent chance of producing children afflicted with the disease.[84] Similar work needs to be done on large populations within the United States so that proper eugenic guidance may be given to the anxious parents of a child with psoriasis.

Limited attempts have been made, without much success, to find observable changes in chromosome patterns of persons with psoriasis. Goldman observed that karyotypes obtained from leukocyte cultures of one psoriatic patient were normal.[57] Hochglaube and Karasek found no change in the number of fine structure of chromosomes observed in tissue culture fibroblasts obtained from two female and one male psoriatic patient.[66]

Clinical Features

Psoriasis is classified in the group of papulosquamous dermatoses. This group of dermatologic diseases has the common denominator of a scaling papule as a primary lesion. Careful inspection of this primary lesion and close observation of the arrangement and distribution of the lesions are helpful in differentiation.

The primary lesion of psoriasis is an erythematous papule, topped by a silvery, micaceous scale which is loosely adherent (Figure 1). When the scale is scraped off, several bleeding points appear (Auspitz sign). While not entirely diagnostic, the presence of the Auspitz sign suggests the possibility of psoriasis.

The primary lesions coalesce to form plaques, which may assume many different patterns. The plaques may be solid, with sharply demarcated borders, and vary from coin size to extensive plaques resembling a chart or map. These large plaques are aptly called geographic and may cover the entire back or chest. Annular plaques, with a raised scaling border and central clearing may develop and assume figurate, gyrate or serpiginous outlines. Symmetry is a characteristic feature of psoriasis. Common sites of involvement are the hair line, (Figure 2), elbows, knees and pre-sacral or intergluteal regions. Patients who have a limited form of the disease are often unaware that they have psoriasis unless it is called to their attention by a relative or physician. More widespread involvement, with significant cosmetic disability, is common. Lesions may appear on any part of the integument. They often evolve into large plaques on the extremities or trunk (Figure 3) that persist for years unless adequately treated (chronic plaque type). The fingernails are commonly involved.

Nail involvement provides considerable assistance in establishing a diagnosis of psoriasis. The palms and soles may be involved, the lesions at



Figure 1.—Widespread psoriatic plaques. Note silvery micaceous scale.

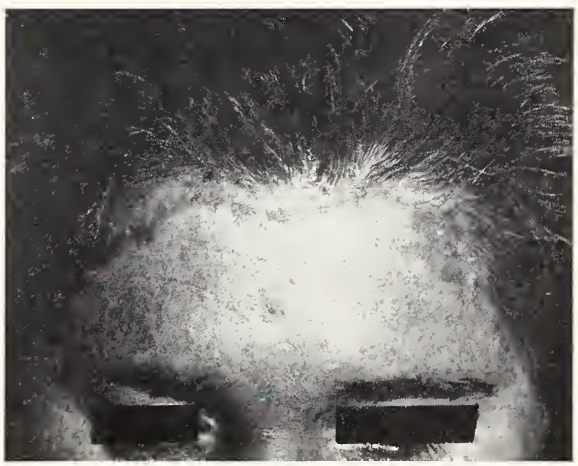


Figure 2.—Typical involvement of the scalp with extension of psoriatic plaques onto forehead.



Figure 3.—Large geographic plaque on trunk. Note sharply demarcated border of plaques.



Figure 4.—An example of "seborrheic" psoriasis, with extensive involvement of the groin.

those sites being pustular or large scaling erythematous plaques. Mucous membrane involvement, although rare, does occur. The glans penis and vulva are the most frequent sites of mucosal psoriatic lesions, but psoriasis of the lips, of the hard and soft palate and of the tongue have all been recognized.[10,89] Stuart, in his review of the ocular manifestations of psoriasis, emphasized that keratitis occurs as a manifestation of psoriasis.[128] It has been our observation that tinea pedis may coexist with psoriasis. "White psoriasis," the sodden, white patches in the interdigital webs of the fingers and toes of psoriatic patients, do not contain fungi, according to Waisman.[139]

Several clinical variants of psoriasis are recognized. Psoriasis may progress to an exfoliative erythroderma in which the entire skin becomes warm, red and scaling. Patients who have psoriatic erythroderma are systematically ill. Their cutaneous blood flow may be increased two-thirds above normal, and high output congestive heart failure may ensue.[53,123] Detailed studies of these patients by Fox demonstrated increased venous pressure with hypervolemia as well as a gross disturbance of body temperature regulation.[53] Psoriasis may present initially as an exfoliative erythroderma, but Roe emphasized that iatrogenic agents often induce this state in psoriatic persons.[105] Withdrawal of systemic corticosteroid therapy, the use of synthetic antimalarial drugs and harsh topical therapy all have been reported to induce psoriatic erythroderma.[29,105,150] Atopic eczema, lymphomas and occasionally drug eruptions can present with a similar appearance. From a review of the literature, Roe estimated that 20 percent of patients with exfoliative erythroderma have underlying psoriasis.[105]

Seborrheic psoriasis (Figure 4) is another clinical variant. The principal areas of involvement are the scalp, retroauricular folds, ears, presternal region, interscapular region, central portion of the face, axillae and groin. This type is commonly mistaken for seborrheic dermatitis, but the presence of characteristic cutaneous lesions or nail changes of psoriasis help to differentiate the two. Psoriasis in the scalp usually forms discrete plaques covered by a silvery scale, while seborrheic dermatitis is diffuse and patchy and has a greasy scale.

The acute guttate form (Figure 5) of psoriasis presents, in younger persons, as an explosive eruption of small teardrop lesions, predominantly over the trunk. Although this form may be the first manifestation of psoriasis, it can appear in a patient with preexisting lesions. The relationship of this clinical variant to preceding tonsillitis has been

recognized since 1916.[149] In a study by Norrlind of 65 patients with acute guttate psoriasis, 64 percent gave a history of upper respiratory infection one to three weeks before the onset of the guttate flare. Of 32 selected patients with acute guttate psoriasis, 56 percent had an elevated antistreptolysin titer (ASO) greater than 200.[90] Whyte and Baughman recently reported that 17 of 20 patients with acute guttate psoriasis had an ASO titer greater than 200 Todd units. These figures contrasted strikingly with an elevation in only 2 percent of 50 patients with the chronic plaque stage of psoriasis. The average age of the guttate group was 28 years, while that of the chronic plaque group was 48 years, confirming Norrlind's figures and the long-held clinical impression that acute guttate psoriasis is a disease of the young.[148] Whyte and Baughman recommend careful observation, throat cultures and prompt treatment should beta streptococcal infections occur in psoriatic patients. Whether or not such preventive measures can modify psoriasis of this type is still an unanswered question.[148]

It has been occasionally observed that in patients with psoriasis of the chronic plaque type an acute guttate flare develops during therapy with widespread topical applications of corticosteroids under occlusive dressings. Knudsen commented on this phenomenon and postulated a pituitary-adrenal axis suppression by the absorbed steroid that reduces circulating levels of endogenous corticosteroids.[74]

As a rule sunlight is beneficial to psoriatic patients, but occasionally a patient with psoriasis is extremely sensitive to ultraviolet radiation. In these patients typical lesions of psoriasis (Figure 6) appear in the sun exposed areas. The psoriasis in these light-sensitive patients is better in the winter and worse in the summer. Bielicky and others have stressed that these patients are more apt to have fairer skins than the patients who are not light-sensitive, and also that their minimal erythema threshold for ultraviolet light is lower than normal.[16] In his experience, patients with the light-sensitive psoriasis benefit from chloroquine therapy, while the lesions in the usual patient with psoriasis are often exacerbated by this drug.[15,17] However, O'Quinn and others administered chloroquine to psoriatic patients who were not light sensitive, and could not demonstrate any exacerbation.[91] It is interesting that the minimal erythema threshold of six patients who were not light sensitive was decreased by 30 seconds or more while they were receiving chloroquine.[91] Bielicky and coworkers used an indirect *in vitro* method to measure blood pentose cycle activity in psoriatic patients and showed that the pentose cycle activity in them was above the normal.[17] There was a tendency for the pentose cycle activity to increase further following six weeks of chloroquine therapy, and there was some correlation between clinical improvement and a decrease in pentose cycle activity, and also between clinical exacerbation and an increase in blood pentose cycle activity during chloroquine therapy.[17] Unfortunately, their results were not statistically significant, but this line of investigation would seem to hold some promise in unravelling the enigma of light sensitivity, psoriasis, and chloroquine therapy.

A variety of clinical types of chronic pustular eruptions of the hands and feet have been described, including pustular psoriasis, acrodermatitis continua, and pustular bacterid. These entities



Figure 5.—Acute psoriasis of guttate type with multiple papules over the buttocks.



Figure 6.—Light-sensitive psoriasis. Note sparing of skin protected by shoulder straps during exposure.

have long plagued the dermatologic literature, and have led both physician and patient into a frustrating search for a focus of infection as a cause for the resistant pustular eruption. Everall evaluated the significance of focal sepsis in 70 patients with intractable pustular eruptions of the hands and feet, and removal of such a focus played little or no part in producing permanent cure.[41] Ingram thought that these entities were all variants of a single reaction pattern, and that psoriatic persons were more susceptible to this reaction than others.[68] In pustular psoriasis, sterile, pustular lesions occur on the palms and soles alone, or in association with plaques or guttate lesions on the glabrous skin. Nail changes are usually present and there is a high degree of association with arthropathy involving the interphalangeal joints. In rare instances, pustular psoriasis may become generalized (von Zumbusch type), with pustular lesions present over the entire integument, accompanied by leukocytosis, fever and other toxic symptoms. Wallace reported a case in which there were recurrent bouts of eruptions of this type, usually associated with infection and steatorrhea.[140] Shelley reported exacerbations of a generalized pustular eruption by use of salicylates.[120] Sulphonamides and phenothiazines have also been noted to produce pustular exacerbations of psoriasis.[2] Systemic corticosteroid therapy has been implicated as one factor that may convert psoriasis of a chronic plaque type into a generalized pustular type.[24] Improvement on therapy with antibiotics has been reported in some cases, but this is not the rule.[24] Cultures from the pustules are sterile, and despite the isolated case reports mentioned, we remain ignorant of the exact cause of this severe form of psoriasis.

The presence of subtle nail changes can be of immeasurable value in establishing the diagnosis of psoriasis in a questionable case. Calvert and coworkers found that 55 percent of 260 patients with psoriasis had nail changes.[22] The commonest change found in the fingernails is tiny "ice-pick" pits which are often grouped. This characteristic pitting of the nails is highly specific for psoriasis, although a few isolated pits may be seen as a normal variant or as a result of past trauma. Spots of greasy, yellowish discoloration are a common finding in psoriatic toenails, and also appear in the fingernails. Onycholysis, or separation of the nail pit distally from its bed, is common (Figure 7). Samman commented that the separated portion



Figure 7.—Typical psoriatic nail involvement: pitting, onycholysis, subungual debris.

of the nail is usually white, but between this and the normally attached nail there is often a yellow margin characteristic of psoriasis.[115] Other changes consist of subungal hyperkeratosis (an accumulation of keratinous debris underneath the nail) as well as transverse and longitudinal ridging; these findings are much less specific, since they also occur secondary to dermatitis, fungus infection, vascular insufficiency and a variety of other conditions. Splinter hemorrhages were found by Calvert and coworkers in half of their psoriatic patients with affected nails, but this occurs only in rare instances.[22] Occasionally one encounters a patient with typical psoriatic nail changes without any other cutaneous findings at the time of initial examination; it is our contention that all of these patients are psoriatic and may well develop typical lesions of psoriasis on the integument if observed closely enough and followed for a long time.

Natural History

The concept of psoriasis as a genetically transmitted disease would seem at first glance inconsistent with the capricious clinical course that psoriasis may take; it is a disease characterized by exacerbations and remissions. For that reason, Farber and Peterson postulated the theory of latent psoriasis.[47] Presumably, the latent period of psoriasis begins near the time of birth and ends when clinical evidence of the disease appears. If clinical remission occurs, then the patient once again enters the latent stage until new lesions appear at some future time.

The factors which convert latent psoriasis into clinical psoriasis are still largely unknown. The

relationship between the acute guttate type of psoriasis and upper respiratory infections with beta streptococcal infection has already been discussed. This may be an example of a complex series of events occurring in genetically fertile soil and elevating the tissues above the threshold which separates the latent from the clinical phases of psoriasis.

Many diverse stimuli which have long been known to aggravate clinically evident psoriasis may at times convert latent psoriasis into clinical psoriasis. Trauma to the skin, such as might be inflicted by a burn or scratch, may result in a typical psoriatic lesion in the site of injury a few days later (the Koebner response). A study of 2,144 patients carried out at Stanford revealed statistical correlations between the course of psoriasis and other events.[43,45] Hellgren, in his study of 255 patients, found 51 percent affected by season of the year, with 22 percent better in summer; nervousness was related to exacerbations in 53 percent.[64] In his survey of psoriasis in the Faroe Islands, Lomholt found similar seasonal variation, but less than 10 percent of the patients reported exacerbations related to nervousness.[84]

Once the clinical phase of psoriasis has begun, there may be a wide fluctuation in severity and extent of involvement. Usually at least a few lesions are persistent, although spontaneous remissions do occur. There may be a transformation of the chronic plaque type to a widespread guttate type, which then evolves back into the chronic plaque type. Church stated that the earlier in life psoriasis appears, the worse the prognosis.[25] Lomholt as well as Farber and Carlsen confirmed this.[44,84] Complete remissions for periods of five years have been reported. Church found that 8 percent of his patients were free of lesions for that period of time, and Lomholt reported that 16.7 percent of his patients were symptom-free for a five-year period.[25,84] Lomholt reported 5.9 percent of his patients were symptom-free for 20 years.[84] These findings support the theory of latent psoriasis. Mild to severe pruritus may be a consequence of the psoriatic process. Lomholt reported that while few of his patients were severely annoyed, 20 percent had constant itching, and an additional 20 percent had itching during acute outbreaks.[84]

Koebner Phenomenon—The Isomorphic Response

In 1887 Heinrich Koebner described the peculiar reaction of psoriatic persons to trauma, a reaction that has since become known as the isomorphic or Koebner response.[75] A wide variety of traumatic stimuli may evoke a psoriatic lesion in previously uninvolved skin. A few examples of the types of trauma provoking this response drawn from patients seen at the Stanford Clinics include: scratches, removal of adhesive tape, venipuncture, lacerations, abrasions, rubbing of brassiere straps, rubbing of wristwatch, girdle, rings and the like.[48] A standard dermatology text contains an illustrative picture of psoriasis appearing in a tattoo, no doubt secondary to contact dermatitis from the tattooing material.[94] A recently observed patient began to have lesions on his palms shortly after taking up sailing (trauma from holding the main sheet line and the tiller).

There is a time lag between the injury and appearance of the psoriatic lesion of approximately 7 to 30 days. Most patients have characteristic lesions within two weeks. In the experience of Farber and coworkers, patients in the florid stage of disease are more likely to have an isomorphic response than those whose disease is static or regressing.[48] Hellgren noted clinical incidence of the isomorphic response in 47 percent of his series; Farber and Carlsen reported an incidence of 40 percent in theirs.[44,64]

Investigators have utilized the isomorphic response as an experimental tool to determine whether the psoriatic lesion has its beginnings in the dermis or the epidermis. Telner and Fekete concluded that the first visible change in a provoked lesion of psoriasis appears in the capillaries.[132] Reinertson was unable to induce an experimental isomorphic response by use of suction to produce dermal capillary rupture, but was successful when he used cellophane stripping or knife blade scraping of the epidermis to the point of minimal bleeding.[101] Farber and coworkers found that the introduction of catgut into the dermis, extensive dermal knife injury, and enzymatic interference with the structural integrity of the dermis did not result in a psoriatic lesion.[35,48] Epidermal scraping to the point of bleeding and Frigiderm freezing produced isomorphic response in a high percentage of the patients studied, but this kind of trauma probably produces both epidermal and dermal injury.[35,48] It would appear that dermal injury alone will not produce an isomorphic response, but combined epidermal and dermal injury will.

Psoriatic Arthritis

The coexistence of psoriasis and arthritis has long been recognized. One series has estimated the incidence of arthritis in psoriatic patients to be 6.7 percent.[81] The North Carolina study revealed an incidence of 2.7 percent in the kindred; this was the same in those affected and unaffected with psoriasis.[1] Lomholt found an over-all incidence of only 1.5 percent in his series, but 4.7 percent of his patients over 40 years of age with psoriasis had arthritis.[84] Farber previously estimated that approximately 10 percent of psoriatic patients have either symptomatic or objective findings of arthritis.[42]

In the past, most authorities classified the arthropathy as rheumatoid arthritis, but in recent years it has become clear that there are significant differences between rheumatoid arthritis and the type of polyarthritis seen in psoriatic patients. The classification of psoriatic polyarthritis has been clarified by Bollet and Turner and by Reed and fellow workers, who have established the following criteria:[19,96,97]

- Psoriatic arthritis begins in the early 30's while rheumatoid arthritis is a disease of middle age.
- Psoriatic arthritis is asymmetrical more often than is rheumatoid arthritis.
- Rheumatoid nodules are absent.
- Males have psoriatic arthritis more often than females, in a ratio of 3:2; the reverse is true in rheumatoid arthritis.
- The agglutination test for rheumatoid factor is negative.
- There is typical involvement of the distal interphalangeal joints in psoriatic arthritis; severe destructive changes are present, and the bone ends appear as if they had been in a pencil sharpener (arthritis mutilans).
- There is a close association between flare-ups of the arthritis and of the psoriasis.
- Psoriatic nail changes are usually present (Figure 8). Other workers have confirmed the absence of rheumatoid factor in psoriatic arthritis.[5,7,63,80,87]

Baker found that the prevalence of psoriasis in Rose-Waaler positive typical rheumatoid arthritis was 1 to 2 percent, the same as in the general population. The prevalence of psoriasis in Rose-Waaler negative, but clinically typical rheumatoid arthritis, was 9 percent, or five times greater than would be expected in the general population. In Rose-Waaler negative polyarthritis that clinically was not typical or rheumatoid arthritis, the prevalence of psoriasis was 20 percent, ten times greater than would be expected in the general population.[5,6] These figures support the contention of other investigators that psoriasis and true rheumatoid arthritis occur together only by coincidence. They further suggest that psoriatic arthritis may often closely mimic rheumatoid arthritis.

Avila and coworkers noted five roentgenologic signs of psoriatic arthritis[4]:

1. Destructive arthritis involving predominantly the distal interphalangeal (I-P) joints of the fingers and the I-P joints of the toes. (Figure 9.)

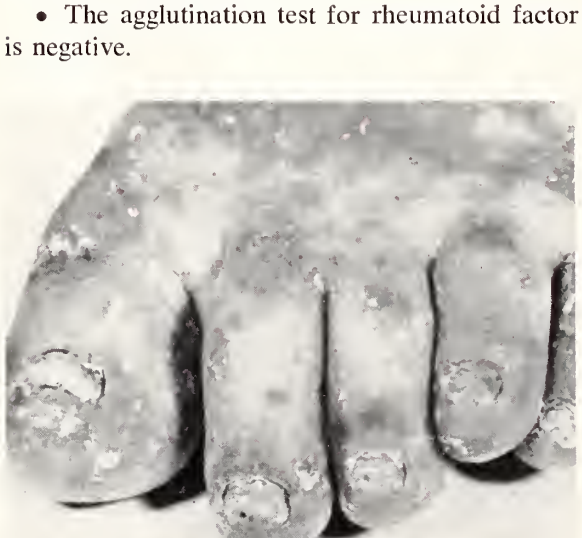


Figure 8.—Psoriatic arthritis. Digits are enlarged, and the fourth toe is shortened. Nail changes are present.

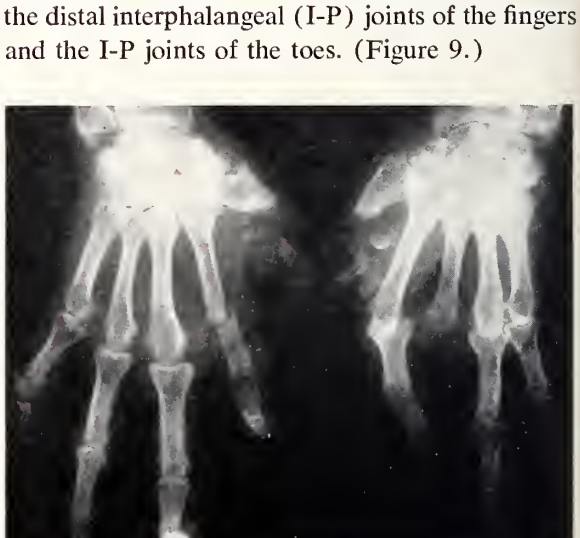


Figure 9.—X-ray film of the hands of a psoriatic patient with arthritis. Note severe destructive changes.

2. Bony ankylosis of the I-P joints of the hands and feet.

3. Destruction of I-P joints of the hands and feet, with abnormally wide joint spaces and sharply demarcated adjacent bony surfaces.

4. Destruction of the I-P joint of the big toe with bony proliferation at base of distal phalanx.

5. Resorption of tufts of distal phalanges of the hands and feet.

In a comparative study of 169 psoriatic patients with joint involvement and 140 patients with rheumatoid arthritis, Lassus and coworkers found no characteristic erosive or osteolytic findings in psoriatic arthritis; however, they did find localization of arthritic changes to the distal I-P joints of the fingers or the I-P joints of the *lateral* toes in the group of patients with psoriasis. In 23 percent of their patients the onset of arthritis preceded the onset of cutaneous lesions.[79]

Baker and coworkers pointed out that 28 percent of their series of psoriatic arthritis patients had sacroilitis.[8] Kaplan and coworkers found a striking incidence of apophyseal sclerosis, apophyseal joint narrowing and anterior ligamentous calcification of the cervical spine, similar to those changes seen in rheumatoid spondylitis.[70] Franks reported one case of acute temperomandibular joint involvement in a psoriatic patient, the involvement then becoming recurrent; flares of the arthritis were associated with flares of the psoriasis.[55]

Nail changes occurred in 83 percent of Baker's series.[8] A detailed study of these patients showed that the severity of nail changes correlated well with the severity of arthritis. Nail changes were not especially related to arthritis in the corresponding terminal I-P joints.[9]

Several investigators recently have called attention to the similarities between the cutaneous eruption (keratodermia blenorrhagica) seen in Reiter's syndrome and psoriasis.[72,86,93,151] In keratodermia blenorrhagica, pustular lesions appear on the soles, with heaped up, crusted lesions on the glabrous skin (rupioid). Wright and Reed studied 12 patients with Reiter's syndrome, in all of whom typical lesions of psoriasis on the glabrous skin either were present at the time the syndrome occurred or developed later.[151] Kahn and Hall followed seven patients with Reiter's syndrome who subsequently exhibited the characteristic features of psoriatic arthritis, some of whom had typical lesions of guttate psoriasis.[72] However, Weinberger and coworkers made no mention of psoriatic lesions on the glabrous skin in 16 patients whom they followed an average of six years.[143] Whether or not Reiter's syndrome is a special form of the psoriatic state is still a moot point. It is of interest that many of the patients observed by Weinberger and coworkers had severe flares of the disease following the administration and withdrawal of corticosteroids.[143] A similar phenomenon has been observed in pustular psoriasis.

Histopathology

The psoriatic lesion is hyperplastic in nature; there is a thickening of the epidermis and an increase in mitotic activity. Although many other cutaneous ailments have similar features, there are histopathologic findings present in the psoriatic lesion which help to differentiate it from other kinds of dermatosis. Unfortunately, the diagnosis may still be open to question even if all the features classically associated with psoriasis are present.

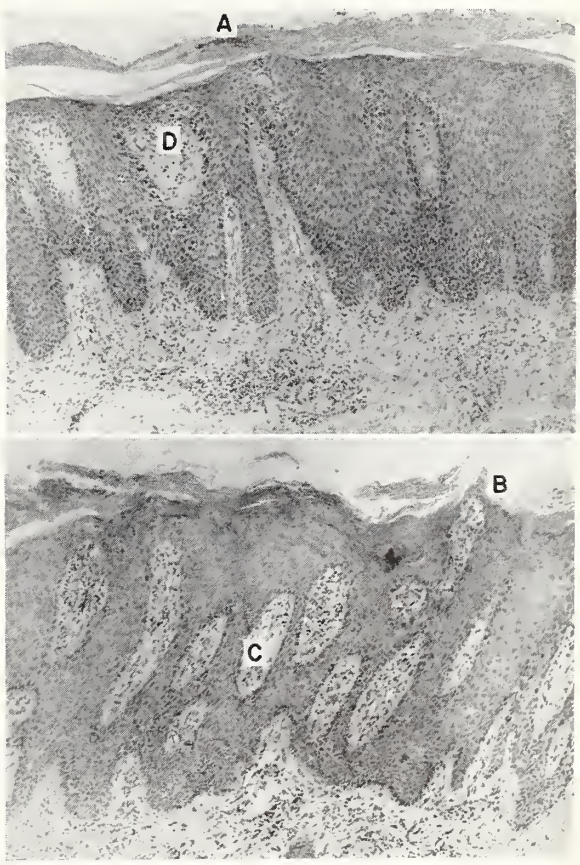


Figure 10.—Photomicrographs of psoriatic lesions. Note parakeratosis and loss of granular layer. Intracorneal collection of neutrophiles at A, suprapapillary thinning at B, dilated capillaries at C, clubbed dermal papilla at D, uniform acanthosis, minimal epidermal edema, sparse epidermal infiltrate, and patchy mononuclear dermal infiltrate.

Helwig thoroughly described the histopathologic features of psoriasis, and Lever presented a concise, accurate description in his book.[65,82] The principal findings (Figure 10) are:

- Hyperkeratosis
- Parakeratosis
- Intracorneal or subcorneal collections of polymorphonuclear leukocytes (Monro microabscesses)
- A diminished or absent granular layer
- Elongation and broadening of rete ridges to an even depth
- Uniform acanthosis (thickening) of the stratum malpighii
- Increased mitotic activity in the lower regions of the epidermis
- Suprapapillary thinning of the stratum malpighii
- Edema and clubbing of dermal papillae that contain dilated blood vessels
- A patchy, scant mononuclear cell infiltrate in the superficial dermis

The stratum corneum is usually decidedly thickened, and contains layered zones of parakeratotic nuclei sandwiched between zones of orthokeratosis. Monro microabscesses are often absent, but almost always a few polymorphonuclear leukocytes can be found sprinkled through the keratin. A peculiar collection of eosinophilic amorphous material is often found in the keratin; this is positively stained by the Periodic-Schiff reagent. This finding is not specific for psoriasis.[30] The uniform thickness of the stratum malpighii is a striking feature and edema or spongiosis is usually absent; if present, edema is often localized in the suprapapillary region.[30] A few polymorphonuclear leukocytes and mononuclear inflammatory cells can be found sprinkled through the epithelium, with denser collections of polymorphonuclear leukocytes in the suprapapillary regions.[30] The granular layer is diminished in thickness and disappears beneath regions of heavy parakeratosis.

Thinning of the epithelium above dermal papillae is not a constant feature. When present, it is thought to be the cause of a positive Auspitz sign because of the proximity of blood vessels to the surface. Broadened, elongated rete pegs extend to an even depth, and mitotic activity is increased in the three lowermost layers of the epidermis.[135] Helwig thought that the strikingly edematous appearance of the clubbed dermal papillae was due to a proliferation of stromal cells, although others disagree.[65] Blood vessels in this region are dilated, tortuous and occasionally show some proliferation of their endothelial cells. Multinucleated endothelial cells have been observed.[30] Dermal papillae contain a few polymorphonuclear leukocytes, but the bulk of the dermal infiltrate is made up of lymphocytes and histiocytes in a perivascular location. A few eosinophiles may be present but plasma cells are rare. The infiltrate is not dense and does not go deeply. Often there are "skip" areas in the dermis where the infiltrate is minimal to absent; this can be helpful in differentiating psoriasis from dermatitis.

An active, well developed lesion of psoriasis contains little pigment in the basal layer, while pigment-laden macrophages in the dermal papillae are abundant.[30] Some observers have noted an increase in mast cells in psoriatic skin when compared with normal controls.[131] Pinkus and Mehregan recently called attention to defects of the basement membrane in the suprapapillary region.[95]

The histopathologic picture of pustular psoriasis shows many of the above features, but spongiosis is prominent; and large collections of polymorphonuclear leukocytes are found in the upper malpighian layer amidst a network of cell-wall remnants (spongiform pustule of Kogoj). Presumably this migrates upward and becomes a Monro microabscess. The Kogoj pustule is also found in the lesion of Reiter's syndrome, and is another point in favor of the association of this syndrome with the psoriatic process.

Kinetics of Hyperplasia in the Psoriatic Lesion

Van Scott and Ekel characterized the type of hyperplasia in the psoriatic lesion by using mitotic counts and volume measurements. They determined that the volume of the epidermis per unit area of skin surface in psoriasis is approximately four times that of uninvolved epidermis. The number of mitotic forms per unit area was 27 times that in uninvolved skin. From these data they calculated a cell turnover time (the time it takes for a cell to progress from the basal layer to the outer part of the stratum corneum) of 96 hours.[135] Rothberg and coworkers[112] calculated a similar turnover time using radioactive glycine-C_{14}, as did Weinstein and Van Scott who employed labeled thymidine.[144] This accelerated rate contrasts with

the normal epidermal turnover time of 26 to 27 days.[112,144] Work by Epstein and Maibach indicates that the turnover time measured above is not the same as total epidermal renewal time; in the normal epidermis, one cell moves from the basal layer to the outer part of the granular layer in 10 to 14 days, but it can take as long as six weeks for all cells to reach the surface.[39]

Biochemistry of the Psoriatic Lesion

Aerobic and anaerobic glycolysis is increased in the psoriatic lesion, and numerous investigators have found elevations of a variety of carbohydrates, lipids, proteins and enzymes.[133] There are conflicting data in the literature that make interpretation of the significance of these findings difficult, and in some instances impossible. Many of the dynamic changes in the psoriatic lesion are not specific and occur in other disorders where the epithelium is undergoing rapid proliferation.

Since the end result of epidermal proliferation appears to be the production of keratin, considerable attention has been focused on the structure of this fibrous protein which makes up the psoriatic scale. Swanbeck used x-ray diffraction techniques to measure the diameter of the protein fibril in psoriatic scale and normal stratum corneum. He found a value of 70 to 100 Å units in psoriatic tissue as compared with a value of 250 Å units in normal skin.[130] Since protein-bound sulfhydryl groups and water soluble protein are decidedly increased in psoriatic scale, it would appear that there may be an interference with the formation of disulfide linkages that prevents normal aggregation of keratin fibrils in the psoriatic stratum corneum.[118] So little is known about the keratinization process that it is difficult to speculate about what has gone wrong to interfere with this bonding. Investigators have looked for abnormal proteins with different amino acid sequences. A number of specific quantitative differences in amino acid composition between psoriatic tissue and normal tissue have been noted, but none of them striking enough to suggest specific genetic alteration with single amino acid substitution to produce an abnormal protein that might account for this altered keratin.[111] An immunoprotein not present in normal epidermis has recently been found in psoriatic scale, but this was also noted in a case of nonpsoriatic erythroderma.[51]

In 1961 Wheatley and Farber called attention to elevated levels of nucleoprotein in psoriatic scale.[146,147] Other workers have confirmed this finding, and Scott recently found 100 times more DNA in psoriatic scale than in normal soft keratin.[118] The presence of parakeratotic nuclei in an area where nuclei are not usually found certainly accounts for some of this excess nucleoprotein, but faulty control of nucleoprotein synthesis with resultant excess of DNA and heightened protein synthesis may account for the hyperplastic psoriatic lesion and the production of abnormal keratin. An extensive survey of the enzymes involved in epidermal glucose metabolism by Halprin and Ohkawara revealed a general increase in all enzymes in the psoriatic plaque with a disproportionate increase in glucose-6-phosphate-dehydrogenase and 6-phospho-gluconate-dehydrogenase.[60] Since these enzymes are concerned with a transformation of glucose-6-phosphate into five carbon sugar phosphates that eventually become ribose phosphate needed for nucleic acid synthesis, the selective increase in these two enzymes might represent an example of a faulty control mechanism.[60] Rippa and Vignalli have found a similar elevation of these two enzymes in psoriatic lesions.[103] Considerable work remains to be done before the significance can be fully evaluated.

Abnormalities in Uninvolved Skin and Other Organ Systems of Psoriatic Patients

Since psoriasis is considered a genetically transmitted disease, the existence of such a dynamic process in the affected part of the psoriatic has led numerous investigators to search for abnormalities in both uninvolved skin and the organism as a whole. Considerable attention has been focused on the psoriatic capillary and circulation. Local increased blood flow (measured by the clearance of radioactive I^{131}) has been demonstrated within the psoriatic plaque.[49] However, studies utilizing digital plethysmography have failed to confirm earlier reports that there was a generalized cutaneous circulatory disturbance in patients with psoriasis vulgaris.[61,88] Holti found abnormalities in clinically unaffected skin of psoriatic persons in its response to histamine, but Eilard and Hellgren found no significant difference between the sensitivity of the unaffected skin sites of psoriatic persons and matched controls to histamine.[36,67] Ross called attention to the abnormal capillary structures present in clinically unaffected skin which resemble those found in psoriatic plaques.[109] When tetracycline is administered to psoriatic patients, significant levels

can be measured in uninvolved skin, while no detectable levels (greater than 0.003 mcg) are found in the skin of normal persons or in the uninvolved skin of patients with dermatitis.[32] It would appear that patients with psoriasis may have an ill-defined abnormality in the microcirculation of uninvolved integument, although the possibility that the uninvolved skin studied may have at one time in the past been involved with psoriasis cannot be excluded.

Enzymes involved in epidermal glucose metabolism including glucose-6-phosphate dehydrogenase have been noted to be at normal levels in the uninvolved skin of psoriatic patients by several investigators.[60,103] However, Ribuffo and Barduagni found an elevation of glucose-6-phosphate dehydrogenase in uninvolved skin of psoriatic patients.[102] Roe called attention to a possible alteration of taurine metabolism in psoriasis.[107] She found that when exogenous taurine was administered to patients with the disease, intense itching developed within one hour, as well as increased scaling and extension of cutaneous lesions. A few of her patients improved on a low taurine diet, but her data are inconclusive.[106,107] Verma found a similar clinical response to exogenous taurine in psoriatic patients, but also noted exacerbation in patients with eczema. He concluded that it is unlikely that taurine ingestion is an etiologic factor in psoriasis.[136] We have been unable to confirm Roe's findings in our patients.

Transepidermal water loss has recently been noted to be increased over the uninvolved skin of psoriatic patients, and this is not the case in patients with dermatitis.[14] Harman reported distinct differences in the inflammatory response of psoriatic uninvolved skin from that observed in normal skin, measured by the Rebuck skin window technique.[62] However, work carried out at Stanford and elsewhere refutes this.[3,78]

Analysis of the immunologic response of psoriatic persons has for the most part produced normal findings. Using a variety of antigens, Landau surveyed a small group of patients and found no difference from a normal control group.[78] Skog and Linder measured auto-antibodies in a large psoriatic group and found a slight correlation between antibody titers and extent of cutaneous involvement, but concluded that formation of skin auto-antibodies seemed to be a chance occurrence.[124] Epstein and Maibach noted that psoriatic patients seem less likely to be sensitized by simple chemicals than normal persons, but immunoelectrophoretic (IGA and IGM) patterns were normal.[40] Other investigators have found elevations of immunoglobulins (IGA and IGM) in psoriatic patients, but this has not been clear cut.[33] Psoriatic skin, both clinically involved and uninvolved, appears to respond normally to autografts, although Clendenning and Van Scott had a high rejection rate in their experiments.[26,83,85] They attributed rejection to the unusual susceptibility of hyperplastic psoriatic tissue to the effects of temporary anoxia.[26]

Mild elevations of acid mucopolysaccharide and hydroxyproline have been found in the urine of psoriatic patients, suggesting mesenchymal involvement.[20] Other workers noted that hydroxyproline is elevated in the urine of patients with many other kinds of dermatosis.[125] Investigators have observed an elevation of glucose-6-phosphate dehydrogenase in red blood cells from psoriatic patients, but the biologic properties of these cells seem to be normal.[102,113] We have discussed earlier in the section on chloroquine the observation by Bielicky and coworkers of an elevation in blood pentose cycle activity in psoriatic patients.[17]

Numerous observers in the past have tried to link psoriasis with diabetes mellitus. One recent study carried out on 103 psoriatic patients with a mean age of 50 revealed that 25 percent had an abnormal glucose tolerance curve; in addition, there was a frequent occurrence of both diabetes and psoriasis in the family histories of the abnormal group.[98] Lomholt found a very low incidence of diabetes mellitus in the psoriatic patients he observed on the Faroe Islands, and cited a low incidence also among Danish psoriatic patients.[84] It would appear that these conditions may coexist in certain populations, but they are not necessarily interdependent.

Uric acid metabolism has been studied extensively in psoriatic patients. Baumann and Jillson found the mean serum uric acid value of male and female patients was significantly higher than the mean of their respective control group.[11] Abele and coworkers found no correlation between serum levels of uric acid and the occurrence of psoriasis in their kindred.[1] Walton and associates found that a few of their psoriatic patients had elevated serum uric acid levels, but even more patients in their control group with other kinds of dermatosis had elevated levels.[141] Eisen and Weissman correlated the serum level of uric acid with the extent of

cutaneous involvement; the more extensively involved patients had higher levels.[38,145] Eisen and Seegmiller measured the incorporation of radioactive labeled glycine into urinary uric acid in patients with psoriasis, patients with gout, and normal controls; all five psoriatic patients studied showed an increased incorporation of glycine.[37] The pattern of uptake was intermediate between the controls and the patients with gout. One psoriatic patient studied, following clinical remission, showed a normal uptake.[37] It would appear that the elevation of serum uric acid in psoriatic patients is simply a result of a pronounced increase in cutaneous nucleic acid synthesis and degradation, and that it is not specific for the psoriatic process. Clinicians should not be led into the trap of labeling a patient with psoriasis, arthritis and elevated serum uric acid as a gouty arthritic.

Earlier studies suggesting an elevation of the serum cholesterol or serum lipids in psoriatic persons have been refuted by recent, well-controlled studies. Benton and coworkers found no significant variation in the serum cholesterol in 176 patients with psoriasis as compared with a normal control group matched for age, sex and body build.[13] Shapiro and associates found no alteration of serum lipoproteins in persons with psoriasis.[119] The North Carolina study revealed no correlation between the incidence of psoriasis and serum cholesterol levels in their kindred.[1]

Therapy

The treatment of psoriasis can be successfully carried out if the patient is highly motivated and cooperates with the physician. Psoriasis is by nature a chronic, recurring disease. Certain measures can result in complete resolution of lesions, but the disease is still present in its latent form and will eventually again become clinically evident. The variable natural history of the disease makes it difficult to evaluate newer therapeutic agents.

A careful explanation of the nature of his illness can be helpful if presented in an encouraging manner. Stressful factors in the environment, excessive weight, and concurrent disease should all be controlled insofar as is possible.

A cardinal rule is to select a topical preparation that the patient will use. Cosmetically unacceptable ointments which remain in the jar give no benefit to the patient and seriously undermine his confidence in the wisdom of his physician.

Topical therapy is the mainstay of the treatment of psoriasis today. Coal tar derivatives, ammoniated mercury and salicylic acid remain important ingredients in the anti-psoriatic armamentarium, although topical corticosteroids, particularly the potent fluorinated steroids, have been welcome additions.

Recent work has shed some light on the biochemical effect of some of the time-tested remedies. Freedberg uses an *in vitro* skin slice system to measure the effect of ammoniated mercury, sulfur, salicylic acid and coal tar solution on the protein synthesis of guinea pig skin. It is interesting that both ammoniated mercury and salicylic acid increased protein synthesis, while coal tar and sulfur caused an inhibition of protein synthesis, after causing an initial slight increase.[56] Freedberg postulated that the latter two compounds interfere with RNA to cause this diminished protein synthesis, although further work needs to be done before this can be accepted.[56] Krebs and Schaltegger showed that dithranol (a coal tar derivative) caused a clear diminution in the activity of glucose-6-phosphate dehydrogenase (it will be recalled that this enzyme has been linked to a possible faulty control mechanism of nucleic acid synthesis in the psoriatic lesion) as well as a reduction of epidermal mitotic figures.[76] Other observers have pointed to a rapid reduction in the thickness of the prickle cell layer following three days of therapy with dithranol, but have called attention to the persistence of the inflammation, capillary abnormalities and parakeratosis.[110,129]

Topical therapy is the treatment of choice for psoriasis of the chronic plaque type. Topical fluorinated steroids have improved the treatment of this stage of the disease, particularly when the agent is applied beneath plastic occlusive dressings held in place for 12 to 24 hours. Apparently a deposit of steroid is formed in the lower regions of the stratum corneum which may persist for as long as a two-week period, slowly diffusing into the cutis.[23,137] Investigators have shown that there is an inhibition of glycolysis and a decrease in the amount of dehydrogenases present caused by the fluorinated corticosteroids; a decrease in mitotic activity has also been reported.[12] These findings may account for the rapid clinical response when lesions are treated in this manner. Clinical remission may be temporary, with rapid recrudescence of lesions a few weeks after therapy is discontinued. Persistent vessel changes have been dem-

onstrated in areas that have clinically cleared; these are anatomic indicators that the lesion has been suppressed, but not cured.[129] Comparative studies have shown that lesions treated with topical fluorinated steroids regress faster than similar lesions treated with coal tar derivatives, but the former recur faster than the latter.[74,129]

When applied over large areas of inflamed skin beneath occlusive dressings, corticosteroids may produce a measurable depression of the pituitary adrenal axis.[73,116] This phenomenon may account for the guttate flare which occasionally occurs in patients undergoing therapy of this type. However, Scoggins and Kliman showed that 10 grams of a 0.01 percent fluocinolone acetonide cream may be applied twice daily beneath occlusive dressings to areas greater than 20 percent of the body surface without producing measurable systemic effects.[117] Atrophic striae have occurred as a sequellae to topical fluorinated steroid therapy with occlusion or when applied without occlusion to intertriginous areas. Miliaria and maceration of the skin can occur from the use of occlusive plastic dressings. In older persons, with severe peripheral vascular disease, ulcerations may occur over the lower extremities as a complication of such a form of therapy.

We have found the application of 5 to 10 percent concentration of liquor carbonis detergens (LCD—a saturated coal tar extract) in a water washable base is a cosmetically suitable and relatively inexpensive preparation for the outpatient management of psoriatic plaques on the glabrous skin. Three to 5 percent salicylic acid may be added to the preparation. For patients who find this preparation messy, ammoniated mercury, 2 to 5 percent, may be substituted for the LCD, although we have found it less effective. Tar baths, using two tablespoons of LCD in the bathwater or a variety of commercially available tar bath preparations, may be employed. Exposure to natural sunlight is also helpful, although the patient must be instructed to build up his exposure time gradually.

Coal tar is a photosensitizer and may cause difficulty in some patients. Mercury can be systematically absorbed from the skin affected with psoriasis; Inman and coworkers found elevated levels in several patients undergoing topical therapy with ammoniated mercury. They recommended that mercury ointments should not be used in patients under five years of age or in pregnant women, and that they should have limited use in patients with a history of nephritis, impaired kidney function or albuminuria.[69] Absorption of topically applied salicylic acid has recently been reviewed by Von Weiss and Lever; in three of their patients with extensive psoriasis acute salicylism developed during treatment.[138] Impairment of renal function is a contraindication; also the physician should be alert for early symptoms of salicylism in patients who apply salicylic acid in an ointment to extensive portions of the body surface.[138] When any of the above agents are used, a small area should first be tested with frequent applications over a 24-hour period to exclude sensitivity.

Psoriasis on certain areas of the body demands special care. Intertriginous areas do not tolerate tar preparations; they fare better with topical steroids. The scalp can be a stubborn area to treat. Tar preparations stain light colored hair, but are well tolerated by some patients. A variety of tar shampoos are commercially available; 10 percent LCD in tincture of green soap is effective. Mineral oil applied beneath a hot towel often helps to remove scales. A corticosteroid lotion covered by a plastic bathing cap during the night also produces good results.

Patients who have significant morbidity from widespread psoriasis benefit enormously from treatment in the hospital. Here the Goeckerman regimen (which consists of frequent applications of crude coal tar in a petrolatum vehicle, daily tar baths and ultraviolet light) may be used over a three- to four-week period to produce a remission that may last as long as a year. We initiate therapy with 1 percent crude coal tar mixed in a zinc oxide-petrolatum base (zinc oxide 30 gms, petrolatum q.s.ad 120 gms) and increase the concentration of crude coal tar to as high as 5 percent. This preparation is applied every two hours during waking hours. The addition of an emulsifier, 0.5 percent polysorbate 80, has been shown to make a more uniform dispersal of the tar when added to the above preparation.[31] Before ultraviolet light therapy, the tar is removed in a tar-oil bath, which leaves a thin film of tar remaining. The light source is a hot quartz lamp, and therapy is begun with a minimal erythema dose (usually 30 seconds exposure at 30 inches distance); the exposure is gradually increased each day by an additional 10 to 15 seconds. Care must be taken not to burn the patient, since a Koebner phenomenon might occur. High concentrations of crude coal tar produce a sterile, chemical folliculitis in hairy regions which

may result in the development of new lesions, (Koebner phenomenon).

The Ingram method of treating psoriasis incorporates 0.2 to 0.8 percent concentrations of anthralin and 0.4 percent concentration of salicylic acid mixed in a base made up of stiff Lassar's paste and paraffin.[27] Application of this paste is made to the individual lesions and the patient is covered with a stockinette. The consistency of the paste confines the anthralin to the lesions and allows the patient to pursue his normal activities. Daily tar bath and ultraviolet light therapy are also used.[27] We have found this method effective when used on patients in the hospital but cumbersome for outpatients.

A suspension of triamcinolone may be injected directly into a localized lesion of psoriasis, with rapid involution of the lesion. Concentrations of 2 to 4 mg per ml are optimal. Higher doses bring a faster response but may produce atrophy, although the latter complication is usually temporary.[92] Small fractionated doses of superficial x-ray (75R) will clear lesions for a short time, but there are many objections to the use of this treatment for benign dermatosis. One study showed that Grenz rays (very low voltage x-ray) in doses of 600 to 1,200R cleared lesions in 33 percent of patients after four weeks, but after three months only 18 percent remained improved.[54] Total body therapy with an electron beam (average dose 2,150 rads) has been used for some patients with severe and intractable psoriasis; lesions involuted for only a short period, with recurrence three to four weeks after therapy.[58]

Acute psoriasis in guttate flare must be approached with caution. It is generally best to avoid specifically active agents and use emollient creams or ointments, such as eucerin cream or hydrophilic ointment. Topical fluorinated steroids may also be used (fluocinolone, flurandrenolone, triamcinolone). Sedation and bed rest are indicated if there is generalized involvement. Systemic corticosteroids and ACTH should not be used in generalized psoriasis of this type because of the severe rebound or even exfoliative erythroderma that may occur when the steroid dosage is reduced or discontinued. Serious complications may follow the use of antimetabolites such as folic acid inhibitors in this type of psoriasis.

Patients with generalized, exfoliative psoriasis (Figure 11) challenge the resourcefulness of the physician. These patients are severely ill and require hospital care. Only bland topical therapy should be used lest the condition be aggravated. Close attention must be paid to the regulation of body temperature, since the diseased skin makes the patient extremely susceptible to subtle changes in environmental temperature. Digitalization and diuretic therapy may be required to manage heart failure. Vitamin therapy may be worth while. Infection is a common complication, manifested by cellulitis, subcutaneous abscesses and lymphangitis. Appropriate cultures followed by vigorous antibiotic therapy should be employed as indicated. Systemic corticosteroids are sometimes useful in this unusual form of psoriasis. We have prescribed prednisone for a short period in the dose range of 40 to 60 mg, or triamcinolone in a dose range of 32 to 48 mg per day and gradually tapered the dose. Methotrexate has been used to manage this kind of psoriasis, but we think its disadvantages outweigh its beneficial effects .



Figure 11.—Exfoliative erythroderma. The entire integument is involved.

Pustular psoriasis of the hands and feet is notoriously stubborn. Topical fluorinated corticosteroids beneath occlusive dressings produce improvement in some cases. Systemic antibiotics have an effect in some cases, but not all. Treatment of the psoriatic nails is also frustrating, although some of our patients have responded to the fluorinated corticosteroids beneath occlusive dressings.

Systemic Therapy

The search for a "magic bullet" that will resolve lesions of psoriasis without disturbing the normal metabolic functions is far from over. Systemic

use of corticosteroids was at first received with great excitement and hope, only to fall into disuse because of the serious long-term side effects and a rebound phenomenon in which new areas of psoriasis appeared. We have already mentioned that there may be a place for systemic corticosteroids in the management of a patient who has severe, widespread exfoliative psoriasis, although not without danger of rebound. Robinson employed long-term low dose triamcinolone therapy (6 mg a day) in the management of resistant pustular psoriasis of the extremities with some success; therapy was carried out for periods of from 6 to 24 months. It is noteworthy that psoriatic lesions on the glabrous skin did not respond to this method of treatment.[104] Indomethacin has been shown to have no effect on the skin lesions of psoriasis.[71] Inorganic arsenic has been employed for decades with effectiveness, although it has fallen into disrepute because of its carcinogenic effects. Fierz reviewed the cases of 262 patients treated previously with inorganic arsenicals; 40 percent of them in later years had keratosis palmaris et plantaris and 8 percent had skin cancer.[50]

There does not appear to be any indication for the use of supplementary vitamin therapy in the routine case of psoriasis. Sneddon showed in a double blind study that a placebo was as effective as Vitamin B_{12} injections in producing improvement in a group of psoriatic patients.[126] A negative Vitamin C balance has been demonstrated to exist in psoriasis, although not severe enough to produce frank deficiency.[134]

In 1951, Richard Gubner and his colleagues observed that patients undergoing therapy for arthritis with aminopterin (a folic acid antagonist) had improvement of psoriatic lesions.[59] Rees and coworkers who pioneered in the use of aminopterin for psoriasis, concluded that the treatment is effective, but not without risk; and that it should be considered only for very severe forms of psoriasis.[99,100]

Methotrexate is now used in place of aminopterin, since the latter is no longer available. This analog of folic acid binds dihydrofolic acid reductase, and thus blocks the synthesis of DNA.[99] It interferes with rapidly reproducing cells, which explains its selective effect on hyperplastic, rapidly replicating psoriatic tissue. It also interferes with other rapidly reproducing cells in blood-forming organs, gastrointestinal mucosa, reproductive organs and, in some circumstances, cells within the reticuloendothelial system.

Since methotrexate is excreted through the kidneys, normal renal function is vital. Close observation of the patient to detect stomatitis or hair fall is mandatory. A complete blood count must be obtained before use of the drug and at frequent intervals while the patient is receiving it. Altered liver function during therapy has been observed; therefore a complete liver profile, including bromsulphalein tests before and during therapy, should be obtained.[18,108,114] The drug should not be given to patients with a history of liver disease, peptic ulcer or renal disease. It is contraindicated in pregnancy. Methotrexate is partially bound to serum albumin, and may be suddenly displaced by para-aminobenzoic acid salicylates or sulfonamides, including oral anti-diabetic agents.[34]

Methotrexate should be regarded as a drug useful for certain persons with disabling psoriasis that is refractory to other therapy. It is a drug best used by dermatologists who are conversant with all methods of care for patients with psoriasis.

Much encouraging progress in the elucidation of the natural history of psoriasis and other fundamental studies has developed with support from the National Institutes of Health and the Hartford Foundation of New York. While comprehensive study is under way, it is increasingly important for the patient to understand the disease. Public information should dispel misconceptions regarding the course of psoriasis and should provide intelligent understanding to the family and friends of patients. In spite of the enigma of the etiology of psoriasis, much can be done by skillful and knowledgeable care.

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REFERENCES

1. Abele, D. C., Dobson, R. L., and Graham, J. B.: Heredity and psoriasis. Study of a large family, Arch. Derm., 88:38-47, 1963.

2. Anonymous: Psoriasis: problems and prospects, Trans. St. Johns Hosp. Derm. Soc., 51:106-108, 1965.

3. Aschheim, E., Chan, T. G., Farber, E. M., and Cox, A. J., Jr.: Cellular response to skin abrasion, J. Invest. Derm., 46:12-15, 1966.

4. Avila, R., Pugh, D. G., Slocumb, C. H., and Winkleman, R. K.: Psoriatic arthritis: A roentgenologic study, Radiology, 75:691-702, 1960.

5. Baker, H.: Epidemiological aspects of psoriasis and arthritis, Brit. J. Derm., 78:249-261, 1966.

6. Baker, H.: Prevalence of psoriasis in polyarthritic patients and their relatives, Ann. Rheum. Dis., 25:229-234, 1966.

7. Baker, H., Golding, D. N., and Thompson, M.: Atypical polyarthritis in psoriatic families, Brit. Med. J., 2:348-352, 10 Aug. 1963.

8. Baker, H., Golding, D. N., and Thompson, M.: Psoriasis and arthritis, Ann. Intern. Med., 58:909-925, 1963.

9. Baker, H., Golding, D. N., and Thompson, M.: The nails in psoriatic arthritis, Brit. J. Derm., 76:549-554, 1964.

10. Baumal, A., Kantor, I., and Sachs, P.: Psoriasis of the lips. Report of a case, Arch. Derm., 84:669-671, 1961.

11. Baumann, R. R., and Jillson, O. F.: Hyperuricemia and psoriasis, J. Invest. Derm., 36:105-107, 1961.

12. Belsan, I., Neumann, E., and Blazkova, B.: Kinetics of glycolysis after fluocinolone acetonide in psoriasis, Acta Dermatovener, 45:297-301, 1965.

13. Benton, J. M., Brown, P. E., and Church, R. E.: The serum-cholesterol in psoriasis, Lancet, 1:583-584, 16 Mar. 1963.

14. Bettley, F. R., and Grice, K. A.: A method for measuring the transepidermal water loss and a means of inactivating sweat glands, Brit. J. Derm., 77:627-638, 1965.

15. Bielicky, T.: Light sensitive psoriasis and antimalarial drugs, J. Invest. Derm., 41:1-2, 1963.

16. Bielicky, T., and Kvicalova, E.: Photosensitive psoriasis, Dermatologica, 129:339-348, 1964.

17. Bielicky, T., Malina, L., and Sonka, J.: Glucose metabolism and clinical alterations in psoriasis under chloroquine therapy, Acta Dermatovener, 46:72-77, 1966.

18. Black, R. L., O'Brien, W. M., Van Scott, E. J., Auerbach, R., Eisen, A. Z., and Bunim, J. J.: Methotrexate therapy in psoriatic arthritis. Double blind study on 21 patients, JAMA, 189:743-747, 1964.

19. Bollet, A. J., and Turner, R. E.: Psoriatic arthritis, Ann. N. Y. Acad. Sci., 73:1013-1019, 1958.

20. Brunish, R., and Sorensen, B.: Urinary excretion of acid mucopolysaccharides and hydroxyproline in psoriasis, Dermatologica, 130:165-172, 1965.

21. Burch, P. R. J., and Rowell, N. R.: Psoriasis: etiological aspects, Acta Dermatovener, 45:366-380, 1965.

22. Calvert, H. T., Smith, M. A., and Wells, R. S.: Psoriasis and the nails, Brit. J. Derm., 75:415-418, 1963.

23. Carr, R. D., and Weiland, R. G.: Corticosteroid reservoir in the stratum corneum, Arch. Derm., 94:81-84, 1966.

24. Champion, R. H.: Generalized pustular psoriasis, Brit. J. Derm., 71:384-391, 1959.

25. Church, R.: The prospect of psoriasis, Brit. J. Derm., 70:139-145, 1958.

26. Clendenning, W. E., and Van Scott, E. J.: Autografts in psoriasis, J. Invest. Derm., 45:46-51, 1965.

27. Comaish, S.: Ingram method of treating psoriasis, Arch. Derm., 92:56-58, 1965.

28. Convit, J.: Investigations of the incidence of psoriasis among Latin American Indians, Proc. of the Int. Cong. of Derm., 1:196, 1962.

29. Cornbleet, T.: Action of synthetic antimalarial drugs on psoriasis, J. Invest. Derm., 26:435-436, 1956.

30. Cox, A. J., Palo Alto, California, personal communication.

31. Cullen, S. I.: Crude coal tar ointments and creams, Arch. Derm., 92: 431-432, 1965.

32. Cullen, S. I., and Crounse, R. G.: Cutaneous pharmacology of the tetracyclines, J. Invest. Derm., 45:263-268, 1965.

33. Danielsen, L.: Immuno-electrophoretic analysis of serum proteins in psoriasis and psoriatic arthritis, Acta Rheum. Scand., 11:112-118, 1965.

34. Dixon, R. L., Henderson, E. S., and Rall, D. P.: Plasma protein binding of methrotrexate and its displacement by various drugs, abstracted, Fed. Proc., 24:454, 1965.

35. Eddy, D. D., Aschheim, E., and Farber, E. M.: Experimental analysis of isomorphic response in psoriasis, Arch. Derm., 89:579-588, 1964.

36. Eilard, U., and Hellgren, L.: Skin sensitivity to histamine in eczema and psoriasis, Intl. Arch. Allergy, 23: 81-86, 1963.

37. Eisen, A. Z., and Seegmiller, J. E.: Uric acid metabolism in psoriasis, J. Clin. Invest., 40:1486-1494, 1961.

38. Eisen, A. Z., and Weissman, S.: Pseudouridine (5-ribosyluracil) excretion in psoriasis, J. Invest. Derm., 39: 35-37, 1962.

39. Epstein, W. L., and Maibach, H. I.: Cell renewal in human epidermis, Arch. Derm., 92:462-468, 1965.

40. Epstein, W. L., and Maibach, H. I.: Immunologic competence of patients receiving cytotoxic drug therapy, Arch. Derm., 91:599-606, 1965.

41. Everall, J.: Intractable pustular eruptions of the hands and feet; a review of 70 patients, Brit. J. Derm., 69:269-272, 1957.

42. Farber, E. M.: The clinical aspects of psoriasis, World Wide Abstracts of General Medicine, 6:8-16, 1963.

43. Farber, E. M., and Bright, R. D.: Psoriasis questionnaire survey, (in press).

44. Farber, E. M., and Carlsen, R. A.: Psoriasis in childhood, Calif. Med., 105:415-420, 1966.

45. Farber, E. M., and Cox, A. J.: Biology of psoriaris, J. Invest. Derm., 49:348-357, 1967.

46. Farber, E. M., Grauer, F., and Zaruba, F.: Racial incidence of psoriasis, Cesk, Derm., 40:289-297, 1965.

47. Farber, E. M., and Peterson, J. B.: Variations in the natural history of psoriasis, Calif. Med., 95:6-11, 1961.

48. Farber, E. M., Roth, R. J., Aschheim, E., Eddy, D. D., and Epinette, W. W.: Role of trauma in isomorphic response in psoriasis, Arch. Derm., 91:246-251, 1965.

49. Ferguson, E. H., and Epstein, W. L.: Clearance of I^{131} injected intralesionally in patients with psoriasis, J. Invest. Derm., 37:441-445, 1961.

50. Fierz, U.: Katamnestiche Untersuchungen uber die Nebenwirkungen der Therapie mit anorganischem Arsen bei Hautkrankheiten, Dermatologica, 131:41-58, 1965.

51. Forsey, R. R., Haberman, H. F., and Langman, J.: Water soluble antigens of psoriatic scale, Arch. Derm., 91:512-518, 1965.

52. Forssman, H.: On question of frequency of psoriasis among population at large, Acta Dermatovener, 27: 492-496, 1947.

53. Fox, R. H., Shuster, S., Williams, R., Marks, J., Goldsmith, R., and Condon, R. E.: Cardiovascular, metabolic, and thermoregulatory disturbances in patients with erythrodermic skin diseases, Brit. Med. J., 5435: 619-622, 6 Mar. 1965.

54. Frain-Bell, W., and Bettley, F. R.: The treatment of psoriasis and eczema with Grenz rays, Brit. J. Derm., 71:379-383, 1959.

55. Franks, A. S. T.: Temperomandibular joint arthrosis associated with psoriasis. Report of a case, Oral Surg., 19:301-303, 1965.

56. Freedberg, I. M.: Effects of local therapeutic agents upon epidermal macromolecular metabolism, J. Invest. Derm., 45:529-538, 1965.

57. Goldman, L., and Owens, P. L.: Chromosome studies in dermatology. Preliminary observations in some congenital and acquired dermatoses and in the effect of radiations with x-ray, Grenz and laser, Acta Dermatovener, 44:68-74, 1964.

58. Grollman, J. H., Bierman, S. M., Ottoman, R. E.,

Morgan, J. E., and Horns, J.: Total-skin electron-beam therapy of lymphoma cutis and generalized psoriasis: Clinical experiences and adverse reactions, Radiology, 87: 908-915, 1966.

59. Gubner, R., August, S., Ginsberg, V.: Therapeutic suppression of tissue reactivity. II. Effect of aminopterin in rheumatoid arthritis and psoriasis, Amer. J. Med. Sci., 221:176-182, 1951.

60. Halprin, K. M., and Ohkawara, A.: Carbohydrate metabolism in psoriasis: an enzymatic study, J. Invest. Derm., 46:51-69, 1966.

61. Hardenstam, C. G.: Digital plethysmography in psoriasis, Acta Dermatovener, 39:41-46, 1959.

62. Harman, R. R. M.: Skin window study of inflammation in psoriasis, Brit. J. Derm., 77:530-531, 1965.

63. Haussler, I., and Jahn, H.: Untersuchungergebnisse bei psoriasis arthropatica, Derm. Wschr., 146:242-253, 1962.

64. Hellgren, L.: Psoriasis. A statistical, clinical, and laboratory investigation of 255 psoriatics and matched healthy controls, Acta Dermatovener, 44:191-207, 1964.

65. Helwig, E. G.: Pathology of psoriasis, Ann. N. Y. Acad. Sci., 73:924-935, 1958.

66. Hochglaube, J., and Karasek, M.: Chromosome studies of normal and psoriatic skin fibroblasts, Arch. Derm., 92:195-199, 1965.

67. Holti, G.: Vascular phenomena diagnostic of latent psoriasis, Brit. J. Derm., 76:503-510, 1964.

68. Ingram, J. T.: Pustular psoriasis, Arch. Derm., 77: 314-318, 1958.

69. Inman, P. M., Gordon, B., and Trinder, P.: Mercury absorption and psoriasis, Brit. Med. J., 2:1202-1206, 24 Nov. 1956.

70. Kaplan, D., Plotz, C. M., Nathanson, L., and Frank, L.: Cervical spine in psoriasis and in psoriatic arthritis, Ann. Rheum. Dis., 23:50-56, 1964.

71. Kern, A. B.: Indomethacin for psoriasis, Arch. Derm., 93:239-240, 1966.

72. Khan, M. Y., and Hall, W. H.: Progression of Reiter's syndrome to psoriatic arthritis, Arch. Intern. Med., 116:911-917, 1965.

73. Kirketerp, M.: Systemic effects of local treatment with fluocinolone acetonide applied under plastic film, Acta Dermatovener, 44:54-62, 1964.

74. Knudsen, E.: Fluocinolone-plastic treatment and traditional treatment in severe psoriasis. A comparative study, Acta Dermatovener, 45:50-58, 1965.

75. Koebner, H.: Zur Aetiologie der Psoriasis, Vischt. Derm., 4:203, 1877.

76. Krebs, A., and Schaltegger, H.: Experimentelle Untersuchungen uber den Wirkungsmechanismus von Chrysarobin und Dithranol bei Psoriasis (Indizien fur eine cytostatische Wirkung an der Epidermis), Dermatologica, 131:1-27, 1965.

77. Lain, E. S.: Skin diseases among full-blooded Indians of Oklahoma, JAMA, 71:168, 1913.

78. Landau, J. W., Gross, B. G., Newcomer, V. D., and Wright, E. T.: Immunological response of patients with psoriasis, Arch. Derm., 91:607-610, 1965.

79. Lassus, A., Mustakallio, K. K., and Laine, V.: Psoriasis arthropathy and rheumatoid arthritis. A roentgenological comparison, Acta Rheum. Scand., 10:62-68, 1964.

80. Lassus, A., Mustakallio, K. K., and Wager, O.: The lack of rheumatoid factor in psoriatic arthritis, Acta Rheum. Scand., 10:69-79, 1964.

81. Leczinsky, C. G.: The incidence of arthropathy in a ten-year series of psoriasis cases, Acta Dermatovener, 28:483-487, 1948.

82. Lever, W. F., Histopathology of the Skin, pp. 119-128, J. B. Lippincott, Co., Philadelphia, 1961.

83. Linder, O., and Skog, E.: Autologous skin grafting in psoriasis. Observations in the first postoperative weeks, Acta Dermatovener, 45:178-185, 1965.

84. Lomholt, G.: Psoriasis: Prevalence, Spontaneous Course and Genetics. G. E. C. Gad, Copenhagen, 1963.

85. Long, P. I., Jr.: Behavior of psoriatic and normal skin transplants, Arch. Derm., 84:593-596, 1961.

86. Maxwell, J. D., Greig, W. R., Boyle, J. A., *et al:* Reiter's syndrome and psoriasis,, Scot. Med. J., 11:14-18, 1966.

87. McEwen, C., Ziff, M., Carmel, P., Ditata, D., and Tanner, M.: The relationship to rheumatoid arthritis of its so-called variants, Arthritis and Rheumatism, 1:481-496, 1958.

88. Moreci, A. P., Farber, E. M., and Sage, R. D.: Digital blood flow rates in psoriasis under normal conditions and in response to local mild ischemia, J. Invest. Derm., 33:113-119, 1959.

89. Norins, A., and Yaffee, H.: Psoriasis of the hard palate: report of a case, Arch. Derm., 76:357-358, 1957.

90. Norrlind, R.: The significance of infections in the origination of psoriasis, Acta Rheum. Scand., 1:135-144, 1955.

91. O'Quinn, S. E., Kennedy, C. B., and Naylor, L. Z.: Psoriasis, ultraviolet light and chloroquine, Arch. Derm., 90:211-216, 1964.

92. Pariser, H., and Murray, P. F.: Intralesional injections of triamcinolone. Effect of different concentrations on psoriatic lesions, Arch. Derm., 87:183-187, 1963.

93. Perry, H. O., and Mayne, J. G.: Psoriasis and Reiter's syndrome, Arch. Derm., 92:129-136, 1965.

94. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: Dermatology, p. 732, W. B. Saunders Co., Philadelphia, 1956.

95. Pinkus, H., and Mehregan, Z.: The primary histologic lesion of seborrheic dermatitis and psoriasis, J. Invest. Derm., 46:109-116, 1966.

96. Reed, W. B.: Psoriatic arthritis. A complete clinical study of 86 patients, Acta Dermatovener, 41:396-403, 1961.

97. Reed, W. B., and Becker, S. W.: Psoriasis and arthritis, Arch. Derm., 81:577-585, 1960.

98. Reeds, R. E., Jr., Fusaro, R. M., and Fisher, I.: Psoriasis vulgaris. I. A clinical survey of the association with diabetes mellitus, Arch. Derm., 89:205-208, 1964.

99. Rees, R. B., Bennett, J. H., Hamlin, E. M., and Maibach, H. I.: Aminopterin for psoriasis. A decade's observation, Arch. Derm., 90:544-552, 1964.

100. Rees, R. B., Bennett, J. H., Maibach, H. I., and Arnold, H. L.: Methotrexate for psoriasis, Arch. Derm., 95:2-11, 1967.

101. Reinertson, R. P.: Vascular trauma and the pathogenesis of the Koebner reaction in psoriasis, J. Invest. Derm., 30:283-286, 1958.

102. Ribuffo, A., and Barduagni, O.: Studio dell'attivita della glucoso-6 fosfatodeidrogenasi nel siero, nei globuli rossi, nelle squame e nella cute sana dello psoriasico, G. Ital. Derm., 106:337-342, 1965.

103. Rippa, M., and Vignali, C.: The levels of enzymes of the oxidative shunt and glycolysis in psoriatic skin, J. Invest. Derm., 45:78-80, 1965.

104. Robinson, T. W. E.: The treatment of pustular dermatoses of the extremities with oral triamcinolone, Brit. J. Derm., 78:158-160, 1966.

105. Roe, D. A.: The nature of exfoliative psoriasis, Cutis, 1:411-420, 1965.

106. Roe, D. A.: Nutrient requirements in psoriasis, New York J. Med., 65:1319-1320, 1965.

107. Roe, D. A., and Weston, M. O.: Potential significance of free taurine in the diet, Nature, 205:287-288, 1965.

108. Roenick, H. H., Jr., Haserick, J. R., and Curtis,

G. H.: Methotrexate for psoriasis. A preliminary report, Cleveland Clin. Quart., 32:211-215, 1965.

109. Ross, J. B.: The psoriatic capillary. Its nature and value in the identification of the unaffected psoriatic, Brit. J. Derm., 76:511-518, 1964.

110. Ross, J. B., McElligott, T. F., and Rout, M.: Histological changes in psoriasis treated with dithranol, Brit. J. Derm., 76:74-80, 1964.

111. Rothberg, S., Crounse, R. G., Davis, L., Avogadro, L., and Lamas, J.: The amino acid composition of protein fractions from normal and abnormal epidermis, J. Invest. Derm., 44:320-325, 1965.

112. Rothberg, S., Crounse, R. G., Lee, J. L.: Glycine-C_{14} incorporation into the proteins of normal stratum corneum and the abnormal stratum corneum of psoriasis, J. Invest. Derm., 37:497-505, 1961.

113. Ruzicka, J., and Kuba, J.: Nektere biologicke vlastnosti erytrocytu u lupenky, Cesk. Derm., 40:145-149, 1965.

114. Ryan, T. J., Vickers, H. R., Salem, S. N., Callender, S. T., and Badenoch, J.: The treatment of psoriasis with folic acid antagonists, Brit. J. Derm., 76:555-564, 1964.

115. Samman, P. D.: The nail in psoriasis, Med. Biol. Illus., 15:148-153, 1965.

116. Scoggins, R. B., and Kliman, B.: Percutaneous absorption of corticosteroids. Systemic effects, New Eng. J. Med., 273:831-840, 1965.

117. Scoggins, R. B., and Kliman, B.: Relative potency of percutaneously absorbed corticosteroids in the suppression of pituitary-adrenal function, J. Invest. Derm., 45:347-355, 1965.

118. Scott, A.: Some aspects of comparative biochemistry of human keratins, Brit. J. Derm., 77:291-301, 1965.

119. Shapiro, E. M., Knox, J. M., and Grundy, S.: Changes in serum lipoproteins in psoriasis, Arch. Derm., 81:940-943, 1960.

120. Shelley, W. B.: Birch pollen and aspirin psoriasis. A study in salicylate hypersensitivity, JAMA, 189:985-988, 1964.

121. Shelley, W. B., and Crissey, J. T.: Classics in Clinical Dermatology, p. 10, Charles C Thomas, Springfield, 1953.

122. Shrank, A. B., and Harman, R. R.: The incidence of skin disease in a Nigerian teaching hospital dermatological clinic, Brit. J. Derm., 78:235-241, 1966.

123. Shuster, S.: High-output cardiac failure from skin disease, Lancet, 1:1338-1340, 22 June 1963.

124. Skog, E., and Linder, O.: Immunologic studies in pathologic conditions of the skin, with special reference to psoriasis, Acta Dermatovener, 45:461-466, 1965.

125. Smith, Q., Rukavina, J. G., and Haaland, E. M.: Urinary hydroxyproline in various diseases, Acta Dermatovener, 45:44-49, 1965.

126. Snedden, I. B.: Vitamin B_{12} in psoriasis, Brit. Med. J., 1:328, 2 Feb. 1963.

127. Steinberg, A. G., Becker, S. W., Jr., Fitzpatrick, T. B., and Kierland, R. R.: Genetic and statistical study of psoriasis, Am. J. Human Genet., 3:267-281, 1951.

128. Stuart, J. A.: Ocular psoriasis, Amer. J. Ophthal., 55:615-617, 1963.

129. Suurmond, D.: Histologic changes in treated and untreated psoriatic lesions, Dermatologica, 131:357-366, 1965.

130. Swanbeck, G.: Macromolecular organization of epidermal keratin. (An x-ray diffraction study of the horny layer from normal, ichthyotic and psoriatic skin), Acta Dermatovener, 39:Supp. 43, 1959.

131. Szabo, E., and Meszaros, C. S.: Die Rolle der Mastocyten in der Histogenese der Psoriasis, Zschr. Haut-Geschl.-Kirkh., 36:373-379, 1964.

132. Telner, P., and Fekete, Z.: The capillary responses in psoriatic skin, J. Invest. Derm., 36:225-230, 1961.

133. Tickner, A.: The biochemistry of psoriasis, Brit. J. Derm., 73:87-98, 1961.

134. Tickner, A., and Basit, A.: Vitamin C and exfoliative dermatitis, Brit. J. Derm., 72:403-408, 1960.

135. Van Scott, E. J., and Ekel, T. M.: Kinetics of hyperplasia in psoriasis, Arch. Derm., 88:373-381, 1963.

136. Verma, B.: Taurine and psoriasis, Indian J. Derm. Vener., 31:105-107, 1965.

137. Vickers, C. F. H.: Existence of reservoir in the stratum corneum. Experimental proof, Arch. Derm., 88: 20-23, 1963.

138. von Weiss, J. F., and Lever, W. F.: Percutaneous salicylic acid intoxication in psoriasis, Arch. Derm., 90: 614-619, 1964.

139. Waisman, M.: Interdigital psoriasis (white psoriasis), Arch. Derm., 84:733-740, 1961.

140. Wallace, H. J.: Generalized pustular psoriasis (von Zumbusch) with episodic hypocalcaemia, Proc. Roy. Soc. Med., 58:425-427, 1965.

141. Walton, R., Block, W. D., and Heyde, J.: A comparative study of uric acid values of whole blood in patients with psoriasis and other dermatoses, J. Invest. Derm., 37:125-133, 1961.

142. Ward, J. H., and Stephens, F. E.: Inheritance of psoriasis in a Utah kindred, Arch. Derm., 84:589-592, 1961.

143. Weinberger, H. W., Ropes, M. W., Kulka, J. P., and Bauer, W.: Reiter's syndrome, clinical and pathological observations. A long-term study of 16 cases, Medicine, 41:35-91, 1962.

144. Weinstein, G. D., and Van Scott, E. J.: Autoradiographic analysis of turnover times of normal and psoriatic epidermis, J. Invest. Derm., 45:257-262, 1965.

145. Weissman, S., Eisen, A. Z., and Karon, M.: Pseudouridine metabolism. II. Urinary excretion in gout, psoriasis, leukemia, and heterozygous oroticaciduria, J. Lab. Clin. Med., 59:852-858, 1962.

146. Wheatley, V. R., and Farber, E. M.: Chemistry of psoriatic scales. II. Further studies of the nucleic acids and their catabolites, J. Invest. Derm., 39:79-89, 1962.

147. Wheatley, V. R., and Farber, E. M.: Studies on the chemical composition of psoriatic scales, J. Invest. Derm., 36:199-211, 1961.

148. Whyte, H. J., and Baughman, R. D.: Acute guttate psoriasis and streptococcal infection, Arch. Derm., 89:350-356, 1964.

149. Winfield, J. M.: Psoriasis as sequel to acute inflammation of the tonsils: clinical note, J. Cutan. Dis., 34:441, 1916.

150. Witten, V. H., and Sulzberger, M. B.: Case Reports: Psoriasis, an interesting and perhaps distinctive response following quinacrine therapy, Arch. Derm., 73: 636-639, 1956.

151. Wright, V., and Reed, W.: The link between Reiter's syndrome and psoriatic arthritis, Ann. Rheum. Dis., 23:12-21, 1964.

MEDICAL STAFF CONFERENCE

Primary Hyperoxaluria

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* Today we shall present a new genetic disease which has been studied extensively in this Medical Center during the past year. The findings in the case of our patient today were presented recently at one of the national research meetings,[5] but have not previously been discussed here. The disease which the patient has is a very rare genetic disorder. It is not of itself of practical importance to a general medical audience because of its rarity. It is presented, however, as a case history of how this type of metabolic disease is recognized and pursued. In this regard we have asked Dr. Hibbard Williams, Assistant Professor of Medicine, to serve as a triple threat man; he is going to present the case summary, and then discuss the disease entity with emphasis on his recent findings concerning the pathogenesis of this disorder.

DR. WILLIAMS:*[1] The patient is a 32-year-old Negro male hotel worker. He was well throughout his life until 1958 when flank pain and dysuria developed and he then was admitted to a hospital, where bilateral nephrolithiasis was found. He was placed on a low calcium diet and felt well until about a year later, when he had a second episode of renal colic. Following the episode he was free of symptoms except for occasional cloudy urine until, in 1965, he was admitted to the Veterans Administration Hospital in San Francisco with severe left renal colic. An intravenous pyelogram demonstrated a stone blocking the left ureter. Left ureterostomy was performed and several small stones were removed. These stones were analyzed and found to contain calcium oxalate. At this time a urinary oxalate determination performed in our laboratory showed the level to be elevated at 140 mg in 24 hours. Since that time the patient has felt well and has continued working. He has had two minor episodes of renal colic with spontaneous passage of small stones on each occasion. There was no family history of renal colic, nephrolithiasis or diabetes mellitus. Results of physical examination were relatively unremarkable. The blood pressure was 110/65 mm of mercury. Abdominal examination was within normal limits; the kidneys were not palpable and there was no costovertebral angle tenderness.

Laboratory data: Hematocrit 40 percent. Leukocyte count was within normal limits, as was the differential smear. Urinalysis demonstrated a trace of protein, pH6.0, specific gravity 1.013. On microscopic examination of the sediment there were numerous calcium oxalate crystals and a few red blood cells. Urine culture on several occasions has been negative. Serum calcium, phosphorus, alkaline phosphatase, creatinine and uric acid were all within normal limits. The 24-hour urine calcium was within normal limits, as was creatinine clearance. Urinary cystine was negative, high voltage electrophoresis of both urine and blood

*Lloyd H. Smith, Jr., M.D., Professor and Chairman of the Department of Medicine.

*[1] Hibbard E. Williams, M.D., Assistant Professor of Medicine.

demonstrated a normal amino acid pattern. Urinary oxalate was 140 mg in 24 hours, (normal 10 to 55), 24-hour urinary glycolate was 32 mg in 24 hours (normal, 15 to 60).

During the past year the patient has been treated with a high fluid and high phosphate intake, and pyridoxine 150 mg per day. Unfortunately he was unable to come to the hospital today. Dr. Youker, will you present the x-ray findings?

DR. YOUKER:*[2] The chest film was within normal limits. The abdominal film shows numerous small calcifications in the right kidney, and an additional radioopacity in the left kidney. These radioopacities are small and extremely dense, suggesting that they are composed of calcium oxalate, the most radioopaque of the materials contributing to renal calculi. In the lower pole of the right kidney these calculi are faceted, which indicates that they are all in the same dilated calyx.

DR. WILLIAMS: In 1792, Alexander Philip Wilson commented in his book, "An Inquiry into the Remote Cause of Urinary Gravel":

> "Here a very important question occurs: does the body by its own powers generate an acid capable of precipitating from the urine, or is such an acid always derived from a cessant diet? Several of the above experiments seem to show that this acid is constantly generated in the body independent of all acids derived from the alimentary canal, and from circumstances already taken notice of, it may pass in great quantity by the kidney."

Today, some 175 years later, I would like to describe two diseases that are caused by the accumulation of organic acids, which are "generated in excess in the urine and passed in great quantity by the kidney."

The subject is primary hyperoxaluria.[2] Although my discussion will concern only a small number of patients and a very rare disease or diseases, it may have broader implications. Approximately two-thirds of all kidney stones contain calcium oxalate. Study of patients similar to the patient presented today may lead to a greater understanding of factors controlling oxalate excretion and thereby benefit patients with oxalate stones of any cause.

To begin, I would like to review the syndrome of primary hyperoxaluria, as it is now known. Primary hyperoxaluria is, first of all, a rather rare genetic disorder. There are some 75 recorded cases in the world literature. It is associated with onset of symptoms early in life, usually between the ages of one and six, and with early death, usually before the age of 20. The major clinical manifestation is recurrent calcium oxalate nephrolithiasis. This is associated with the familiar symptoms of flank pain, dysuria and recurrent urinary tract infection. Nephrocalcinosis also occurs, as does progressive renal failure, which usually leads to death at an early age. The term *oxalosis* refers to the extrarenal deposits of calcium oxalate. These are not specific for primary hyperoxaluria, for they have been found in conditions other than hyperoxaluria. In patients who have died with hyperoxaluria there does seem to be a predilection for calcium oxalate deposition in the myocardium, in the genitourinary system and in the bone marrow. These are rarely of any clinical significance. Two cases have been described with complete heart block, presumably due to calcium oxalate deposition in the conduction system of the heart. The disease is inherited presumably by an autosomal recessive mode of inheritance, but at the present time no definitive heterozygote defect can be demonstrated.

The diagnosis of primary hyperoxaluria is based on the demonstration of an elevated urinary oxalate level. Normal excretion is approximately 10 to 55 mg in 24 hours. In patients with primary hyperoxaluria the excretion of urinary oxalate varies between 150 and 400 mg in 24 hours — approximately three to ten times normal. Besides oxalate, two other organic acids, glycolic acid and glyoxylic acid, are excreted in excess in patients with this syndrome.[3]

Chart 1 is an outline of the synthetic pathways of oxalic acid. Oxalate itself represents a metabolic cul-de-sac. It is not metabolized. All radio-

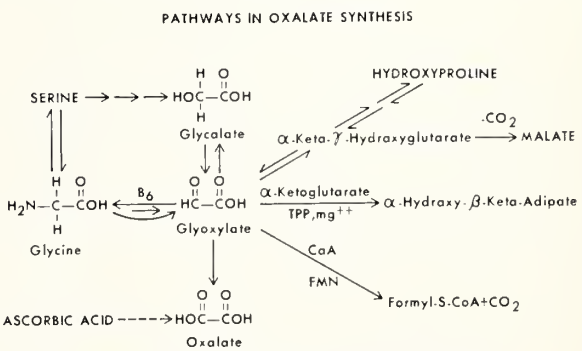


Chart 1.—Biosynthetic pathway of oxalate.

*[2] James E. Youker, M.D., Associate Professor of Radiology.

active oxalate administered to a normal person is recovered unchanged in the urine. Previous studies in patients with hyperoxaluria have demonstrated that oxalate is overproduced from its immediate precursor, glyoxylate. As was previously mentioned, both glyoxylate and glycolate are increased in the urine in patients with hyperoxaluria. Previous studies[1] from Dr. Smith's laboratory have demonstrated a defect in the metabolism of glyoxylate in these patients, which accounts for the increased synthesis and excretion of oxalate.

Glyoxylate has three major pathways of metabolism: transamination to glycine, reduction to glycolate, and reaction with alpha-ketoglutarate to form the compound alpha-hydroxy-beta-keto-adipate. Since glycolate is increased in the urine in patients with hyperoxaluria, the reduction of glyoxylate to glycolate is unimpaired in patients with hyperoxaluria. In the past year we have studied the transamination of glyoxylate to glycine in tissue from four patients with hyperoxaluria, and have found this reaction to be normal.[8] Therefore, we focused our attention on the remaining pathway of metabolism of glyoxalate, controlled by a specific carboligase enzyme. In five patients with primary hyperoxaluria, this enzyme was diminished in cytoplasmic fractions from liver, spleen and kidney.[4] Therefore this enzymatic block in the conversion of glyoxylate to alpha-hydroxy-beta-keto-adipate represents the metabolic error in hyperoxaluria, leading to accumulation of glyoxylate behind the block, and subsequent increased synthesis and excretion of oxalate.

In summary, primary hyperoxaluria is a rare genetic disorder, characterized by recurrent calcium oxalate nephrolithiasis, leading to chronic renal failure and death at an early age. Increased amounts of oxalic, glyoxylic and glycolic acids are found in the urine. Previous studies have demonstrated a defect in metabolism of glyoxylate in this syndrome, and the enzyme defect appears to be a deficiency of a specific carboligase important in glyoxylate metabolism.

I would like to return to the case presented today. The patient was referred to us because of calcium oxalate nephrolithiasis, and, as noted, the urinary oxalate excretion was found to be elevated at 140 mg in 24 hours. This was high enough to be commensurate with a diagnosis of primary hyperoxaluria.

It is customary in this laboratory when an elevated oxalate is found, to carry out a urinary glycolate determination to confirm the diagnosis of primary hyperoxaluria. In the present case two interesting things occurred when this measurement was attempted.

First of all, the absolute level of glycolate was normal, a finding which separated this patient from other patients with primary hyperoxaluria. The second finding is related to the method of measuring urinary glycolate. In order to measure glycolate, a relatively specific color test is used on certain fractions of the urine. When this was performed on urine from today's patient an abnormal color was noted. We therefore began to investigate the reason for this abnormal color, and the first approach to this was through paper chromatography.

Figure 1 represents a paper chromatogram of some urine fractions after column chromatography. On the left is a urine sample from a normal person. The lower spot is unidentified, the upper spot is glycolic acid. The middle urine sample is from a patient with primary hyperoxaluria. The sample on the far right represents the urine of the patient in the present case. A faint glycolic acid spot is discernable, and adjacent to it and overlapping it somewhat is a rather large spot which obviously explained the problems we had had in performing the glycolic acid color test. Here, in fact, was a new compound in the urine which was not found in the urine of other patients with primary hyperoxaluria, nor was it found in the urine of normal subjects, of patients with idiopathic hypercalciuria, or of patients with renal tubular acidosis. At about this same time, we were fortunate to obtain from England urine specimens from two children whom Dr. Smith had studied four years previously. These were siblings, aged eight and ten, who had had nephrolithiasis since infancy. Both had hyperoxaluria but normal levels of glycolate. Paper chromatography of urine fractions from both patients yielded the same abnormal spot as just described in the urine of the patient in today's case.

Our attention was focused on the identification of this abnormal compound. By a variety of techniques including column and paper chromatography, specific color reaction, substrate specificity and derivative analysis, this compound was identified as glyceric acid. Through the kindness of Dr. John Craig of the Department of Pharmaceutical Chemistry the compound was found to exist en-

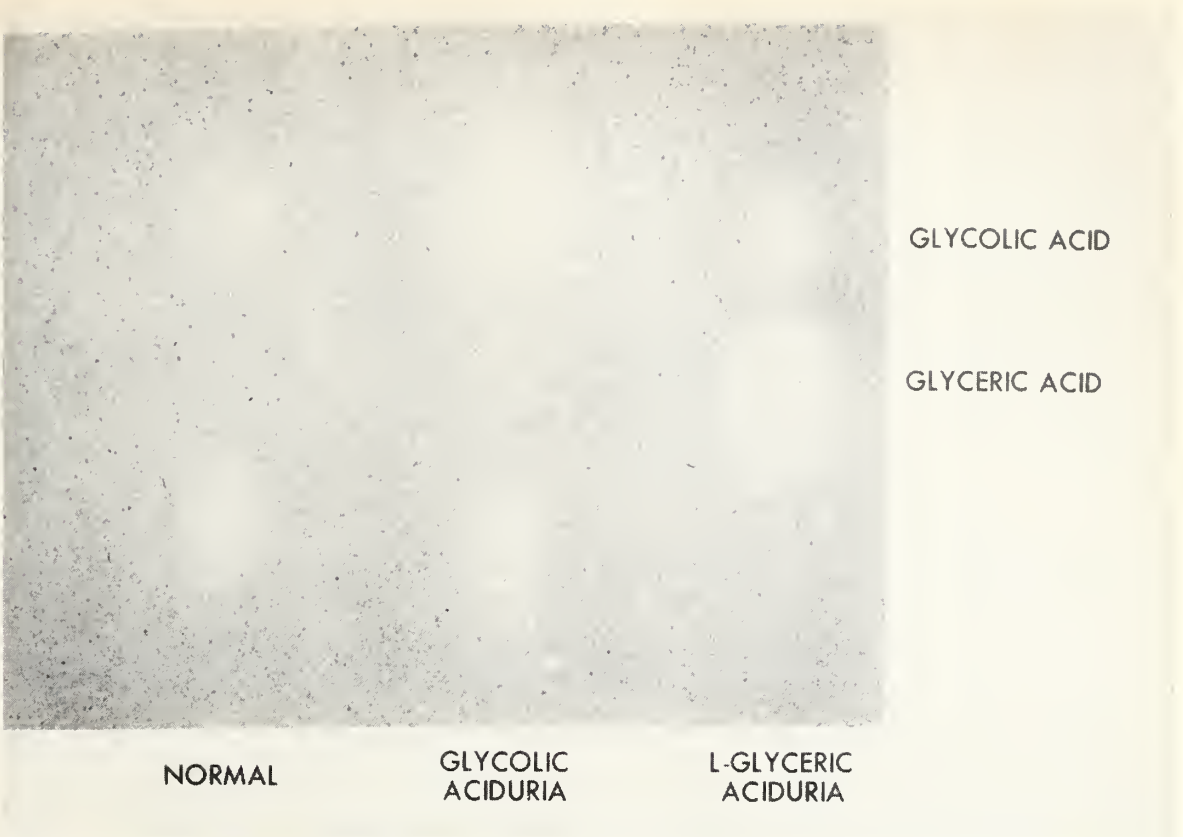
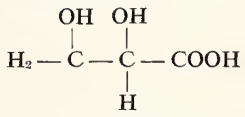


Figure 1.—Paper chromatogram of urine fractions from a normal subject and patients with primary hyperoxaluria. (See text.)

tirely as the L-stereoisomer. The chemical structure of this compound is shown below:



By an isotope dilution technique it was possible to measure the total amount of glyceric acid being excreted.[7] In the three patients with this new syndrome, glyceric acid excretion varied between 196 and 638 mg in 24 hours.

We were left with two rather major questions at this point. First, why was glyceric acid present in the urine, and second what was the association with primary hyperoxaluria? The metabolic pathways involving glyceric acid are shown in Chart 2. D-glyceric acid is an intermediate in the pathway of serine metabolism. Serine may be transaminated to the compound, hydroxy-pyruvate, which is reduced to D-glycerate, which in turn is converted to 2-phosphoglycerate. D-glycerate, then is an intermediate metabolite on the gluconeogenic pathway of serine. Hydroxypyruvate can also be reduced to L-glyceric acid in the presence of lactic dehydrogenase. Since only L-glyceric acid was found in urine, a metabolic block in the conversion of hydroxypyruvate to D-glycerate could explain the increased synthesis and excretion of L-glycerate in these patients.

In order to test this hypothesis, C^{14}-labeled hydroxypyruvate was administered to the patient in our hospital, and over 15 percent of the radioactively labeled material was recovered in urinary glycerate, a finding which demonstrated that

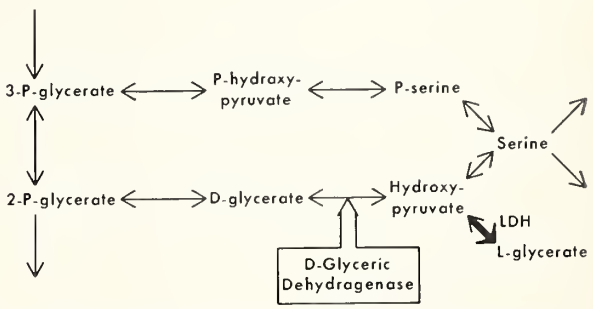


Chart 2.—Metabolic pathways involving glyceric acid. LDH = lactic dehydrogenase.

hydroxypyruvate was in fact a precursor of urinary L-glycerate in this patient.[6] We therefore focused our attention on the enzyme reaction controlling the conversion of hydroxypyruvate to D-glyceric acid, that is, D-glyceric dehydrogenase. The results of the assay of this enzyme in leukocytes from normal subjects and the three patients whose urine we had, are shown in Table 1. As can be seen from this table, no detectable enzyme activity was found in the leukocytes of these three patients. We feel, therefore, that the metabolic defect in L-glyceric aciduria represents a hereditary deficiency of the enzyme D-glyceric dehydrogenase. In this situation hydroxypyruvate accumulates, and in the presence of lactic dehydrogenase it is reduced to L-glycerate which is then excreted in the urine in large amounts. This finding explains the increased glycerate excretion but we had yet to explain the reason for the hyperoxaluria.

There is evidence in plants and bacteria that the enzyme, D-glyceric hydrogenase is similar, if not identical to, the enzyme which controls the reduction of glyoxylate to glycolate. If this is in fact the case, then a deficiency of this enzyme would lead to a block in the oxidation of glyoxylate to glycolate (Chart 1). Glyoxylate would accumulate and this would account for the increased synthesis and excretion of oxalate in the urine of these patients. This is currently our working hypothesis but we have no definitive proof that this is indeed the case.

In summary, L-glyceric aciduria is a rare genetic disease, associated with recurrent calcium oxalate nephrolithiasis. Urinary oxalate is increased but glycolate is normal. L-glyceric acid is found in large amounts in the urine. The enzyme defect represents a deficiency of D-glyceric dehydrogenase.

The differentiation of primary hyperoxaluria from this new syndrome is shown in Table 2. Type 1 is referred to as glycolic aciduria, and type 2 as L-glyceric aciduria. Both are rather rare, and both are characterized by the same clinical manifestation — recurrent calcium oxalate nephrolithiasis. In type 1, oxalic, glycolic and glyoxylic acids are increased in the urine, and the disease is caused by a deficiency of the enzyme 2-oxo-glutarate glyoxylate carboligase. In type 2, L-glyceric and oxalic acids are excreted in the urine in excess, but glycolic acid excretion is normal. A deficiency of D-glyceric dehydrogenase represents the metabolic basis for this type. The differentiation of the two types can be made only by the determination of the urinary organic acids or by demonstration of the specific enzyme deficiency.

We know of no ill effects from glyceric acid accumulation. Therefore treatment is directed toward the hyperoxaluria. Treatment is similar in both types of primary hyperoxaluria — increased fluid intake to decrease the concentration of solutes in the urine, high phosphate intake to inhibit crystal formation, and pyridoxine in doses of 150 mg per day. Pyridoxine is a co-factor important in glyoxylate metabolism, and we have some evidence to suggest that pyridoxine in rather large doses may decrease oxalate excretion in patients with hyperoxaluria.

In conclusion, I would like to relate to you a comment which was traced to a response of the oracle at Delphi, which was given to Polycrates as the best means of finding a treasure buried by Xerxes' general, Mardonius, on the field at Plateia. The oracle reputedly said, "Leave no stone unturned."

DR. SMITH: I don't know how to respond to that last lithic pun. There is time for questions or comments concerning this rather rare disease and its investigation.

DR. FUDENBERG:*[3] How many children are in the family and what is the sex distribution? I gather all important data have been obtained from males.

TABLE 1.—*Leukocyte D-glyceric dehydrogenase activity*

Subject	*Enzyme activity in mμ moles/mg prot./hr.*
Normal Range	12.2-24.3
Mean	18.2
Patients with L-Glyceric aciduria	
Subject patient	0
*10-year-old child	0
* 8-year-old child	0

*Two English children, mentioned in text, from whom urine specimens were available.

TABLE 2.—*Differentiation of two types of primary hyperoxaluria*

Type I	(Glycolic aciduria)
	Clinically recurrent nephrolithiasis
	Urinary organic acids—oxalic and glycolic
	Enzyme defect.—2-oxo-glutarate: glyoxylate carboligase
Type II	(L-glyceric aciduria)
	Clinically recurrent nephrolithiasis
	Urinary organic acids—oxalic and glyceric
	Enzyme defect—D-glyceric dehydrogenase

*[3]H. Hugh Fudenberg, M.D., Professor of Medicine.

DR. WILLIAMS: No, I am sorry I did not specify. There are two sons and one daughter in the family, all affected.

DR. FUDENBERG: Do you plan to do studies on relatives?

DR. WILLIAMS: Yes, we have blood specimens from the parents of the two English children. The activity of the enzyme is low in the mother's leukocytes; in the father's leukocytes it is low normal but still within the normal range.

Editor's follow-up: Shortly after presentation of the case at the staff conference, the patient was admitted to hospital because of acute diabetic ketoacidosis. He responded promptly to insulin and is now being treated with daily insulin therapy. He has had no further episodes of renal colic. The relationship of the diabetes mellitus to his other hereditary disease is as yet unknown.

REFERENCES

1. Frederick, E. W., Rabkin, M. T., Ritchie, R. H., Jr., and Smith, L. H., Jr.: Studies on primary hyperoxaluria. I. In vivo demonstration of a defect in glyoxylate metabolism, New Eng. J. Med., 269:821-829, 1963.

2. Hockaday, T. D. R., Clayton, J. E., Frederick, E. W., and Smith, L. H., Jr.: Primary hyperproxaluria, Medicine, 43:315-345, 1964.

3. Hockaday, T. D. R., Frederick, E. W., Clayton, J. E., and Smith, L. H., Jr.: Studies on primary hyperoxaluria. II. Urinary oxalate, glycolate, and glyoxylate measurement by isotope dilution method, J. Lab. Clin. Med., 65: 677-687.

4. Koch, J., Stokstad, E. L. R., Williams, H. E., and Smith, L. H., Jr.: Deficiency of 2-oxo-glutarate: glyoxylate carboligase activity in primary hyperoxaluria, Proc. Nat'l Acad. Sci., 57:1123-1129, 1967.

5. Williams, H. E., Koch, J., and Smith, L. H., Jr.: L-glyceric aciduria and glycolic aciduria: Two genetic variants of primary hyperoxaluria (abstract), J. Clin. Invest., 46:1133, 1967.

6. Williams, H. E., and Smith, L. H., Jr.: L-glyceric aciduria. A new genetic variant of primary hyperoxaluria, New Eng. J. Med., 278:233-239, 1968.

7. Williams, H. E., and Smith, L. H., Jr.: Identification and determination of glyceric acid in urine, J. Lab. Clin. Med., 71:495-500, 1968.

8. Williams, H. E., Wilson, K. M., and Smith, L. H., Jr.: Studies on primary hyperoxaluria. III. Transamination reactions of glycine and glyoxylate, J. Lab. Clin. Med., 70:494-502, 1967.

A State Medical Association on the Move

ROBERT L. THOMAS, *Executive Director, California Medical Association*

A FULL-FLEDGED RESEARCH DEPARTMENT that provides current socio-economic data for well informed planning for the role of medicine in California; an educational subsidiary that not only pays its own way, but last year provided more than $112,500 for medical education, and a clearinghouse for postgraduate courses that can provide instant information on almost every continuing education course scheduled to be held in California during the next five years—these are only three of the forward-looking programs the California Medical Association has developed and is vitally concerned with in this age of emphasis on health care.

When a handful of family doctors founded a state medical association for California in 1856, they established the constitutional purpose that continues to provide a solid basis for these and the myriad of other activities carried on by today's 23,000-member CMA:

> "To promote the science and art of medicine, the protection of public health, and the betterment of the medical profession."

In that purpose the present-day California physician recognizes his growing responsibility to lead the way in solving health problems facing the public, and through his local medical society and the California Medical Association, he is meeting this obligation.

The CMA also is meeting the needs of the individual physician. Through a committee/commission and Council structure that involves hundreds of physicians, the problems become known and solutions are explored, discussed, decided upon and carried out.

As Executive Director of this growing, dynamic organization, I must admit a certain amount of pride in the accomplishments of the CMA. The thousands of physician-hours devoted to CMA programs are resulting in healthier, safer Californians, and a state in which a physician can be proud to carry on the tradition of his profession. It has been said that California is leading the way for Medicine in the United States. If this is so, the credit must be divided between the progressive, pioneer doctors of early California, whose goals are as appropriate now as they were in 1856, and the California physicians of the 20th century who have continued to look toward the future.

While some of the programs of the CMA are noteworthy because they are unique in their conception, others are outstanding for the degree of their development. Both deserve comment when one is selecting outstanding CMA accomplishments for discussion.

CMA Council

The Council of the CMA, which is responsible for managing the affairs of the organization, implementing the policies approved by the CMA House of Delegates at its annual meeting and determining CMA policies between annual meetings, usually meets ten times each year in regular session. The composition of the Council is geographical, numerically uniform and representative of all major fields of practice of California physicians.

By inviting representatives of other health-oriented organizations, officials of state agencies concerned with public health and deans of medical schools to each of its regular meetings, the Council maintains constant contact and communication with them. During the past year, attendance and interest of these organizations in the meetings of the Council have indicated their desire to maintain and build the liaison that has been developed.

Reprint requests to: 693 Sutter Street, San Francisco 94102.

Bureau of Research and Planning

CMA was the first state medical association to develop a full-scale research component, its Bureau of Research and Planning, staffed by the Division of Socio-Economics and Research. CMA relies heavily upon studies made by the bureau and our research staff to guide its policy decisions and action programs.

Professional liability coverage, one of the most pressing problems of California physicians, recently was the subject of one of the bureau's surveys. The research determined types of coverage physicians carry, premium rates, and which are the major carriers in the state. The information gathered is being used to draft and support new malpractice legislation being sponsored by CMA in the California legislature.

The bureau is continuing a semi-annual survey of changes in physicians' fees that was begun in 1962. A random sample of 1,000 physicians supplies data about usual and customary fees for 27 selected procedures, from which a fee index is computed.

A recent study of the attitudes and habits of California physicians with regard to cigaret smoking received a considerable amount of publicity in the news media. This study was funded by the State Department of Public Health as an aid to the Inter-Agency Council on Smoking and Health.

The CMA has a long history of concern for continuing physician education, and the research staff is cooperating with the Committee on Continuing Education to conduct a three-year census to compile extensive information about formal continuing education courses, and another survey will determine if continuing medical education programs currently offered are meeting the needs of physicians.

Results of many of the CMA studies are published in monthly *Socio-Economic Reports.*

Audio-Digest Foundation

It has been 15 years since the CMA House of Delegates saw sufficient promise in a fledgling postgraduate enterprise called Audio-Digest Foundation to adopt it as a nonprofit subsidiary. Since then, it has grown from a local, small-scale experiment with weekly taped reports from medical journals and meetings for general physicians to twice-a-month subscription services for seven specialties. The number of subscribers now is about 15,000; and since the tapes often are listened to by groups, the total number of listeners is estimated at 50,000. Like CMA, Audio-Digest is looking forward to the future; it already has cartridge tapes available to play on automobile stereo tape equipment, and has begun experimenting with videotape production.

Almost half a million dollars has been contributed by Audio-Digest to medical education since its inception in 1953. As an editorial writer in CALIFORNIA MEDICINE observed some years ago, "Lo: a benign cycle. Medical education is broadened as the number of subscribers increases, and the more subscribers the more revenues, and the more revenues the greater the cash contributions in support of medical education." A truly benign cycle.

Postgraduate Clearinghouse

CMA does more than sponsor its own postgraduate programs. It has a department that serves as a statewide center for coordination of postgraduate medical education—the focal point for *all* organizations in the state that sponsor continuing education courses in medicine. These groups call upon CMA to bring their programs to the attention of physicians *and* to coordinate their programs by resolving conflicts in time, subject matter and location. Last year in California, almost 400 scientific meetings and postgraduate courses rendered 6,756 hours of instruction.

In addition, CMA publishes a detailed chronological listing of each available educational opportunity in *What Goes On,* which is mailed nine times a year to every physician and medical organization in California and Hawaii. Hospitals and county medical societies receive *Medical Dates Bulletin* — a poster-size chronological listing of courses and meetings projected over a six-month period.

Physician Placement

One of the most active physician placement services in the country is operated by the CMA. An average of one physician is placed in a practice every three days through its bulletin, *Opportunities for Practice in California.* This bi-monthly publication has a circulation of about 3,000, going to California hospitals with residency programs, to county medical societies and to medical schools throughout the country. A copy also is sent to each newly licensed California physician, and about 1,500 are distributed bi-monthly to individuals and organizations upon request.

Professional Liability

The rising cost of medical malpractice insurance continues to be a problem in California, as it is throughout the United States. The California Medical Association is taking positive steps to solve the problem, however, and this spring, has had introduced into the state legislature a package of six bills that should lead to a better "professional liability atmosphere" in California.

The bills would:

- Provide for a separate trial of the defense of the statute of limitations before any other issue in the case can be tried, upon motion of either party.
- Place upon the plaintiff the burden of proving the defendant's negligence, and would establish that injury alone does not constitute either the presumption or inference of negligence.
- Extend the present concept of privileged communications to the proceedings and/or records of medical review committees of local medical societies and hospital staffs.
- Require that the time limit for commencement of an action against a physician begin with the date of the alleged wrongful act unless fraud or intentional concealment is proven.
- Provide that any advance payment by an insurance carrier to an injured party could not be construed as an admission of liability.

In addition, CMA is contemplating the submission of legislation that would set reasonable limits for damages under personal injury awards to insure that premium rates for this type of coverage will not become prohibitive; and that would set some boundaries on the doctrine of "informed consent."

CMA also has sponsored, with the California Hospital Association, a statewide workshop to develop constructive solutions for the problems. Conclusions from the workshop will provide the outline for a series of regional professional liability workshops for physicians to discuss recommendations and encourage implementation where feasible.

The Scientific Board

A 36-member Scientific Board that is responsible for all educational and scientific activities of the CMA is another unique element in the structure of CMA. The board, formed in 1962, brings together a representative from each of the 18 scientific sections of the CMA, and 18 members-at-large representing broad categories of medicine, including internal medicine, surgery, general practice, obstetrics and gynecology, pediatrics and neurology and psychiatry. Any branch or field of medicine may be included in the broad categories. In this way the board draws together elements that otherwise tend to be divergent or even at cross purposes.

Eighteen board members are ex officio members of the House of Delegates and one member of its executive committee is a member of the CMA Council.

Specific responsibilities of the board include planning the annual scientific assembly of the CMA; sponsoring continuing medical education and publication of CALIFORNIA MEDICINE. The board also serves as a source of scientific information for CMA members, the House of Delegates, CMA Council, and commissions and committees and the general public.

Mental Health

The State Department of Mental Hygiene and the CMA have been working together toward better care for the mentally ill in California for a number of years. Four years ago, the SDMH requested CMA to survey California's mental facilities. A team of 81 CMA members conducted an 18-month examination and made 230 recommendations, which were accepted by the department for implementation.

Again last year, CMA offered its services for an independent study of the same 14 institutions after critical reports of their operations stirred serious repercussions throughout the state. The CMA's evaluation brought almost immediate action by the Governor to improve conditions at the 14 hospitals.

In other areas of mental health, the CMA has long encouraged communities to utilize and improve their local facilities for mental health treatment. The Short-Doyle Act — supported by the CMA — provides for establishment of local programs with the consultation of the SDMH in planning and initiating approved mental health efforts. It is based on the concept that the archaic custom of isolating the mentally ill in remote custodial asylums must be replaced by effective community-operated programs of rehabilitative treatment.

Medical Staff Surveys

Because CMA believes that communities ought to be assured that their local hospital medical staffs receive continuous review by practicing physicians, it became the first medical association in the nation

to formalize a plan for medical self-government and self-evaluation. In the program, practicing physicians from CMA's Medical Staff Survey teams join local community physicians to evaluate the care rendered and reviewed by hospital medical staffs. The California Hospital Association has made the survey a provision of membership as of 1 January 1969, and by the end of June of this year, 525 of California's 542 acute, short-term hospital medical staffs had requested and received staff surveys of their professional conduct under this program.

The state also has used the teams' services to determine hospitals eligible to participate in the Title 19 program of Medicare.

Government Relations

Liaison with federal and state government is recognized by CMA as a vital component of an effective medical organization today; and to fulfill that role, CMA has a full-fledged Division of Government Relations. In addition, CMA works very closely with the Public Health League (an organization that keeps state legislators informed of CMA's position on health legislation) and with CALPAC (California Volunteers for Political Action).

The Division of Government Relations employs two staff men in Sacramento, the state capital, and three at the CMA office in San Francisco. The division develops and maintains relationships with government officials, and coordinates CMA committee programs that are in response to federal or state law or are administered by a state agency, bureau or department.

The division is not only responsible for keeping tabs on existing government health care programs, but also for maintaining current information on legislative proposals; analyzing legislative proposals in relation to their effect on medical care; informing the CMA of legislative developments; making arrangements for CMA testimony before legislative fact-finding bodies; recommending initiation of legislation by CMA; preparing CMA-sponsored legislation, and a myriad of other activities.

The division also is responsible for activities that affect the professional welfare of CMA members, such as professional liability, group disability insurance and administration of the Keogh retirement plan for physicians in California.

Research Library

The CMA maintains one of only two libraries in the United States limited to socio-medical economics—and according to available comparisons, the CMA library is the most comprehensive. Included in its subject matter are health insurance, health manpower, Medicare, hospital medical staff relationships, medical education, public assistance medical care, social insurance, public health, mental health and medical sociology.

The collection consists of approximately 3,500 monographs and 275 periodicals, and by continuous weeding it is kept current: two years is the usual time limit, with only a few exceptions.

The library also indexes and abstracts all actions taken by the CMA Council and House of Delegates; within the past year, the library began storing this information on computer tapes so it can be supplemented and modified without retyping the entire body of material. The new system will provide a reference tool that will make CMA official policies more accessible and more easily related to current actions under consideration.

The library is used most extensively by the CMA Bureau of Research and Planning, but it serves all CMA members, commissions and committees upon request.

Maternal and Infant Mortality

For more than ten years, five CMA regional committees, aided by special consultants provided by the State Department of Public Health, have reviewed every reported maternal death in California. The information gained from these studies is used for professional and lay education throughout the state.

In instances where the committee feels there were avoidable factors in maternal deaths, or when especially commendable management is apparent, educational letters are sent by registered, to-addressee-only mail, to the attending physicians and/or hospital administrators concerned. To date, 320 letters have been sent. This procedure has been accepted, even to the event of replies indicating corrective action being taken and the use of the reports for educational purposes.

An in-depth study of infant deaths resulting from hemolytic disease of the newborn was recently completed. The study was initiated to improve management of this disease, which is fatal to approximately 200 infants in California each year. A study of bacterial meningitis in infants and

children has been planned to follow the hemolytic disease studies.

Health Tips

In 1961 CMA launched its lay health education series, *Health Tips*. Physicians donate their services to the series by choosing topics, providing basic information and reviewing all publications prior to their release to the public. Subjects range from accidental poisoning to venereal disease.

Health Tips are distributed monthly to 2,139 school personnel; 273 newspapers (including large metropolitan dailies and United Press International, as well as small community weeklies); 104 employee publications, 42 labor publications, 19 farm publications, 113 health agencies and 961 miscellaneous outlets. The total circulation of 3,651 (all by request) is an increase of 58 percent over one year ago.

Descriptions of the positive, action programs of the CMA and its network of organizational and individual liaisons could go on almost indefinitely. Not even touched upon in this report are CMA activities that have improved the workmen's compensation program in California; that have taken a strong public stand against cigaret smoking; that sponsor conferences for the many organizations endeavoring to upgrade occupational health; that have improved medical care in extended care facilities; that are helping communities prepare for emergencies through disaster medical care programs; that are preparing a special study on chloramphenicol, and that have rallied to reduce the health manpower shortage in California.

Reflected in all the programs of the California Medical Association are its willingness to recognize problems and tackle them, its dedicated, well informed leadership by physicians, its well-coordinated programs and its readiness to cooperate with allied health organizations, educators and government. All its surge forward is summed in an *attitude* that is achieving for all of California the goals to which the members of the CMA aspired 112 years ago.

LOCATING A VESICOVAGINAL FISTULA

"I have a little trick which has worked very well for me in trying to locate a vesicovaginal fistula. It's very simple; you put a Foley catheter in the vagina and distend the balloon. It doesn't have to fit airtight. Put a sphygmomanometer bulb at the end of your Foley catheter and have a nurse pump it while you are cystoscoping the patient with some water in the bladder. You will see little bubbles coming up from the floor of the bladder which will then pinpoint the vesicovaginal fistula for you. Also if there is more than one, it will help you to diagnose that."

—Robert O. Pearman, M.D., Encino
Audio-Digest *Obstetrics and Gynecology*, Vol. 14, No. 22

A History of Leadership

HOWARD HASSARD, *San Francisco*

WHEN DR. MALCOLM TODD was installed recently as the CMA's newest president, he called on his fellow physicians to "act now to gain leadership in the larger arena of social and economic change. . . . When we fail to exert this leadership," he added, "others who are less qualified will do it for us."

It is difficult to quarrel with President Todd's words, except in one small detail. Where he said, ". . . act now to gain leadership . . ." he might have said, ". . . retain leadership. . . ." The record shows that the CMA has for many years provided a truly notable leadership in the fields Dr. Todd stresses. Indeed, this record of leadership has been so outstanding that in the area of relations with government the Association's reputation is national. The CMA has established precedents that have been followed by many other medical organizations throughout the country.

Almost 40 years ago, the late Chester H. Rowell, once the noted editor and publisher of the San Francisco *Chronicle,* looking on from a relatively unprejudiced viewpoint, said: "In legislative matters the medical profession of California has set an example that other states may profitably follow."

Since that statement was made, in the 1930's, many states have indeed followed California's example, and there is no question that even the American Medical Association has been influenced.

There is an impression, particularly in lay circles, that organized medicine is always against things, in opposition to anything that might disturb the status quo. The record, as briefly outlined in the paragraphs that follow, will show that this simply has not been true of the CMA's relationship with government and the voters in California. Much of the record is one of positive action, ranging from the initiation of bills from which grew Blue Shield to legislation protecting the public against all manner of quackery. The "mainstream" concept of medical care embodied in the present Medi-Cal program originated in the CMA, and the association helped to develop the bill which was finally enacted into law.

For almost half a century, CMA has had an active Committee on Legislation with strong, well-informed leadership. Among the earliest of its chairmen was Dr. Junius B. Harris. Dr. Dwight Murray followed Dr. Harris in that position, serving until he was drawn away to become president of the American Medical Association. The vigil now is kept by the incumbent chairman, Dr. Dan O. Kilroy.

In all its dealings with proposed legislation, whether initiated by itself or others, the test applied by CMA is simply this: "Is it good for the patient?" If the answer is "yes," then CMA supports.

Advanced Thinking in Legislation

Advanced thinking has been consistently typical of the Association's legislative record. More than ten years ago the CMA helped get written into California law provisions covering the legal aspects of transplanting organs and other tissue from one human to another—a subject that is now much in the current news.

The beginnings go back to much more than a mere ten years ago. The first clearly defined move by CMA in the political field occurred in 1917, during the incumbency of Governor Hiram Johnson, famed for his "liberal" leanings and his boast that he kicked the Southern Pacific out of California politics. He had early in his term appointed a commission to study the health needs of the state. That commission came up with a recommendation for a state-wide compulsory health insurance plan, modeled after the Prussian system. It seems likely that Johnson's eyes were on the White House, and he was bent on making a nation-wide reputation

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out of Sacramento. Governor Johnson happily adopted the idea, and in November 1918, it appeared on the ballot in the form of a constitutional amendment. Due in great part to the active opposition of the CMA and its members, the measure was defeated by more than two to one.

The next major battle of the ballots came in 1922, when the chiropractors, osteopaths and anti-vivisectionists succeeded in qualifying initiative designed to set up separate licensing boards for chiropractors and osteopaths and to impede scientific research. This time medicine did not fare too well. The anti-vivisection measure lost but the separate licensing board initiatives won. Since then there has seldom been a year in which the chiropractors, the naturopaths or other quasi-medical groups have not made some legislative efforts to obtain special status and to foist their fringe ideas on the public. All such moves have been defeated, and the public interest has been served by the CMA, since many such bills would have permitted these ill-trained practitioners to practice even major surgery without legal restraint. A giant stride forward occurred in 1961 and 1962 when medicine and osteopathy unified under one board, one degree and one license. This required an initiative measure, which was passed by an almost three to one vote in November 1962.

In the late 1920's it became evident to forward-looking physicians that medicine in California faced an endless and continuing task if its ideas were to be protected against various quacks. California, ever a utopia for the get-rich-quick racketeer, swarmed with quacks, faddists, and cultists. It became apparent that a permanent organization headquartered in Sacramento was needed to sound the alarm and carry on the fight. (Lobbying is a perfectly legitimate and honorable function in a democratic government. Only its occasional misuse has given it a sometimes bad name.)

Public Health League

A number of such organizations were established within and without the Association during the late 1920's. Finally, in 1932, the best of these became the Public Health League of California, with the redoubtable Ben Read as its guiding genius. It might be well to note some of the League's more significant achievements:

- Despite strong and continuing pressure, the chiropractors and others still cannot practice medicine and surgery.
- The state has no research-stifling anti-vivisection law.
- California physicians have not been forced to practice within the confines of a compulsory health plan.
- The League's proud record shows up in quiet epitaphs to hundreds of bad bills: "defeated," "killed in committee," "tabled in committee."

In 1933 a special meeting of the CMA House of Delegates was convened to discuss a voluntary hospital plan proposed by the Alameda County unit. After much vigorous debate, what might have been the beginning of Blue Cross was voted down. In the following year, the CMA House, influenced by an influx of young liberals, voted to support a compulsory health insurance bill then in the legislature. Due in good part to opposition from labor and farm lobbies, the bill never got out of committee. While this instance of support of compulsory medicine conflicts with long term CMA policy and may even make some of today's physicians wince, it would be inaccurate to pretend it never happened. The explanation is relatively simple. California, like the rest of the nation—and the world—was in the depth of the Great Depression, and physicians are as fond of eating regularly as anyone else. In the next year — 1936 — the House of Delegates voted overwhelmingly in favor of the principle of voluntary medical and hospital insurance plans. In 1937 the House had drafted and sponsored a bill which would have permitted county medical societies to establish their own pre-paid plans. But the time was not ripe for the foundation concept and the bill failed to emerge from committee.

The Olson Years

Governor Culbert Olson, an avowed political radical, was elected in November 1938. He had promised the voters to sponsor compulsory health insurance legislation. Stirred by the threat, the CMA Council submitted to the House of Delegates in January 1939, the outline of a plan for a prepayment service corporation. The House voted it into effect, and thus was born what was to become California Physicians' Service — now California Blue Shield. In that year also Governor Olson had introduced in the legislature his plan for a statewide compulsory plan for medical care. The CMA's vigorous opposition—based in good part on a plea that its own plan be first given a trial—carried the day. In 1941 a bill to put a legal stamp of approval on the CMA voluntary plan passed the

legislature. Olson, who had moved on to other things, apparently forgot what his own plan had been and signed the bill.

The voluntary plan which was to become CPS required special enabling legislation because it was a new concept which would have required more money for basic capital than the CMA had available. The bill, which was passed by the legislature, permitted the plan to start without the usually required capital, and the involved physicians agreed to limit their reimbursement to the amount in the pool formed by pre-paid premiums. Thus, CPS started on a gamble by physicians and on a shoestring in premiums. Other groups have since taken advantage of that legislation. One example is the California Dental Service.

The Warren Plan

The next major period of political activity for the CMA came with the election of Governor Earl Warren in 1942. It seems clear in retrospect that Warren also had his eyes on the Presidency, and hoped to be elected on the issue of socialized medicine. In December 1944, Warren asked permission to appear before the CMA Council and was invited to do so. He told the CMA leaders that he was going to give his full support to a bill calling for a state-wide compulsory health plan. The Governor noted that his bill was certain to have the strong support of organized labor, and hence that some day it would inevitably pass. His siren song was a suggestion that CMA would be wise to get in early and help him shape the bill. The argument was if compulsory medicine is inevitable, then why not have it shaped and controlled by physicians.

The Council heard the Governor out but would not commit itself. Immediately it called a special session of the House of Delegates to consider the matter—around Christmas-time of 1944. By a surprisingly slim majority, the House turned down the Governor's offer. But in a realistic effort to solve a real problem the Council then decided to support a bill which would establish a voluntary health plan, to be supported by voluntary payroll deduction, with payments credited against the employee portion of the unemployment tax. For six months the battle raged in the legislature, with organized labor and Governor Warren on one side, the CMA, the aforementioned Public Health League, the Chamber of Commerce, and the many interests of industry and agriculture on the other. So close was the fight that at one point the Governor's plan lost by only one vote—39 to 38—in the Assembly. Finally the battle ended in an unbreakable stalemate.

Governor Warren did not give up easily. In 1947 a bill for compulsory hospital insurance once more was introduced into the legislature. Again California physicians mounted the barricades. They were satisfied that if this bill passed, state control of medicine would surely follow. And again, thanks to the CMA and the Public Health League, this bill never emerged from committee. Then only did Warren give up. He went on to run for the Vice-Presidency with Dewey in 1948.

CMA Advocacy

That was the last of the big political "spectaculars." But, in each year the CMA and the Public Health League have carried on the continuing work of upholding the integrity of medical practice, of protecting the welfare of the public and of advancing the cause of both patient and physician in a changing world. For example, the CMA created a mechanism for periodic statewide conferences of public health officers, thus substantially enhancing the high quality of public health in the state. The CMA strongly supported the Short-Doyle Act, which helped bring the care of the mentally ill out of hopeless wards of isolated state hospitals and into modern community facilities nearer home and family. The concept of eye banks was pioneered by CMA in 1947, possibly because the country's first corneal transplant was done in San Francisco. In 1957 the CMA sponsored the first and model law legalizing the right of an individual to donate his body or any parts of it for transplant—at a time when human organ transplants were no more than a medical research dream.

Most recently, the Association worked successfully to change state public assistance medical care so that patients were shifted from county hospitals into the mainstream of medical care. One result, long strongly recommended by CMA, has been to bring free choice of physician and greater convenience of hospitalization to the medically indigent.

Many other examples could be given. But this much of a history will suffice to indicate why it is that wherever modern medicine is practiced the California Medical Association is considered an innovator and a leader in the field of medical-government relations. There is every reason to believe that this good reputation will continue to be deserved.

In the Forefront

Comprehensive Health Planning in San Diego

JOSEPH W. TELFORD, M.D., *San Diego*

WHEN P.L. 89-749—providing for Comprehensive Health Planning—became effective 1 July 1967, a very active and informed Hospital and Health Facilities Planning Council together with the San Diego County Medical Society, the Community Welfare Council and the Public Health Department decided that it was time to ask the citizens, both the health professionals and the consumers, what they wanted to do about implementation of the law in our area. It was obvious to the leadership of these organizations, and to many others, that if this new law ever began to be as all-inclusive, and "comprehensive," as it was written, it was destined to affect every citizen in some way.

The leadership of the organizations mentioned sent a letter signed by their presidents to about 60 "health leaders" requesting that they attend a conference on 11 July 1967. The program of this conference was set up to:

- Inform related interests about P.L. 89-749.
- Inform concerned organizations about the most recent developments in comprehensive health planning at the national and state levels.
- Begin discussions related to how comprehensive health planning might be developed in this region. (It was noted that in view of health planning already under way there, Imperial County might properly be included with San Diego County for this program.)

San Diego County has natural boundaries and the Mexican border, a fact that automatically makes the county an "area." Imperial County is linked to San Diego by many ties and especially in the medical field. It is anticipated that Imperial will take steps to join San Diego in its Comprehensive Health Planning Association before 1 July 1968. With no boundary arguments, the initial organization of the association was made easier than in many sections where geography was not so obliging.

At the first conference, the Regional Health Director of Region IX, Dr. R. Leslie Smith, discussed the national and regional roles of the Public Health Service. The then director of California's State Department of Public Health, Dr. Lester Breslow, outlined the current status of implementation of the law at the state level. Following this orientation the conference appointed a steering committee which was directed to make a recommendation as to the structuring which should be adopted in the San Diego area to implement the legislation. To insure a broad view, the steering committee included representatives of the medical society, voluntary health organizations, the mental health and mental retardation fields, the San Diego County Board of Supervisors, the director of the State Department of Public Health, a superintendent from the Junior College system, a member of the County Planning Department, a hospital administrator, a representative from the new University of California School of Medicine at San Diego, the president of the Community Welfare Council and an attorney. Since I was serving as the temporary chairman for the organization efforts, I was chosen to serve as the chairman of the steering committee. The committee was interested and productive and it met many times before reporting.

The obvious immediate question confronting the steering committee was: Shall an existing organization become the areawide comprehensive health organization? The Community Welfare Council indicated it would accept the job. The Hospital and Health Facilities Planning Council

would also—reluctantly. The Department of Public Health made clear that it did not wish to serve as the mechanism for implementation. After study of this problem, it became obvious to the committee that no existing organization in our area was really precisely fitted to become the Comprehensive Health Planning group. A review of the five areas of involvement under the law—(1) Health Facilities and Services, (2) Health Manpower, (3) Mental Health and Retardation, (4) Environmental Health, (5) Personal Health Services—emphasized the meaning of "comprehensive" and pointed the need for a new organization to undertake the task.

The steering committee recommendations to the original organizing group of individuals and organizations interested in health care and implementation of the law were accepted. The recommendations were that:

- An independent, non-profit corporation be established with a board of directors of not fewer than 33 voting members.
- The board of directors conduct the business of the new corporation and select its staff.
- As required by the law, a majority of the board of directors be consumers.
- Guidelines be established for the selection of the board of directors so that there would be consideration of socio-economic groups, geographic location, ethnic groups, health disciplines, health education, business, industry, labor and government.
- Authority be given to the steering committee to designate the first board of directors.
- A mechanism be created to stagger the terms of members of the board of directors.

The steering committee report was the foundation for organizing actions. These actions were the incorporation of the new organization, the preparation of the by-laws and submission of a grant application to the Federal Government.

The selection and designation of the first board of directors was made after soliciting nominees from voluntary health and welfare organizations and government agencies. The selection was a time-consuming job, and I feel that it was done democratically and well.

The organizational meeting of the new board of directors was held 4 December 1967. The Board was briefed on the progress that had been made to date. The attorney member explained the ramifications of the articles of incorporation and the by-laws. Officers were elected. The officers were appointed as a sub-committee to work with the staff from the existing Hospital and Health Facilities Planning Council and the Community Welfare Council in the preparation of a grant application. Liaison with the Imperial County organization was established. Board members indicated their preference as to committee assignments. With these actions, it was obvious that the Comprehensive Health Planning Association of San Diego (and probably Imperial) County was successfully launched.

The required preliminary steps for the presentation of a grant application under section 314 (b) of Public Law 89-749 were fulfilled. The planning grant application was approved by the State Health Planning Council on 26 February with funds to be available starting 1 July.

The board of directors has employed an executive director, who will assume his duties officially 1 July 1968. In the meantime, he is attending our meetings and, like all of us who are concerned about Comprehensive Health Planning, he too is struggling through the self-education routine so vital to the success of the planning process.

We were indeed fortunate to have the complete cooperation of the staff people from the San Diego County Medical Society, the Department of Public Health, the Hospital and Health Facilities Planning Council and the Community Welfare Council. These organizations, recognizing the scope of the law, have contributed and continue to contribute unselfishly to see that we give birth to a healthy "comprehensive" infant, knowing full well that the infant will probably become a giant very soon.

The programs of work for the various committees are rapidly shaping up and Comprehensive Health Planning is now starting. The following outline presents some of the outstanding problems and objectives of our committees. It is recognized that there are many more areas of involvement, but we have made a big beginning.

1. ***Hospital and Health Facilities and Service Planning***
 1. Strengthen existing planning.
 2. More involvement of local governments.
 3. Planning for the proper extended care facilities.

4. Planning for modern concept of progressive medical care.

5. Involvement of the consumers into shaping of the health care system.

6. Developing coordinated master plans from the individual hospitals.

II. *Health Manpower*

1. Further coordinate our area's education system for medical and para-medical personnel needs.

2. Develop a local Health Manpower Council.

3. Redirect the education of practicing physicians more toward care of sick people, and a little less toward research.

4. Reevaluate use of personnel and reduce waste of health man-hours.

5. Give attention to making the entire health field attractive, remunerative and challenging to prospective recruits.

6. Consider the feasibility of pooling certain health manpower in specified health service areas in the interest of adequate care and promoting economies.

III. *Mental Health and Retardation*

In this field, effective coordination, long-range planning and programming have been relatively ineffective and, for practical purposes, totally inadequate. Planning for our future in these fields is unlimited.

1. Better coordination with the California Short-Doyle program.

2. Study and recommend upon the objectives of the voluntary organizations that are disease-oriented—multiple sclerosis, cerebral palsy, etc.

3. Scrutiny of the outpatient care programs for mental patients.

4. Coordinated, long-range planning in these fields.

IV. *Environmental Health*

1. Assist local governments in our area to establish an effective environmental health organization to meet new legislative requirements.

2. Stand ready to assist in the health aspects of air pollution, noise and solid waste problems.

3. Act as the organizing catalyst for industry, labor, the military and the public in a program of coordination on environmental health problems.

4. Assist in the development of an occupational health program for our area.

5. In concert with our Public Health Department, attack the health problems relative to our proximity to Mexico.

V. *Personal Health Services*

1. Serve as the agency to implement the study and action necessary to meet health needs in depressed areas in our jurisdiction.

2. Review and make recommendations as to the efficiency of the outpatient services and home health care programs associated with our hospitals and extended care facilities.

3. Improve our emergency services.

4. Maintain close liaison with the Regional Medical Programs, with special reference to medical services in the areas of heart disease, cancer and stroke.

5. Help with the formation of an information and referral center to serve the health needs of individual patients.

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California Medicine

EDITORIAL

Welcome AMA

CALIFORNIA MEDICINE welcomes the American Medical Association to San Francisco for its 117th Annual Convention. This welcome is a warm one and it is not only to San Francisco but to all of California and the West. You have come periodically since 1871 and have watched us wrestle with our growth and our problems. Your initial California convention, also in San Francisco, was held soon after the transcontinental railroads were completed. It proved to be a potent stimulus to organized medicine in California which has been restlessly growing and generally thriving since that occasion.

The editors of CALIFORNIA MEDICINE and the Council of the California Medical Association take pleasure in presenting this special issue of our Journal as a gift to physician registrants at this AMA convention in San Francisco. While each issue of this monthly Journal strives to reflect the increasingly important scientific, socio-economic and political achievements of medicine in the West, and also to discuss constructively many other scientific and social problems which remain yet to be resolved, this particular number has been especially structured to provide informative and useful fare for physicians who have come from everywhere, and who would perhaps like to take another reading on what's going on in California and the West — as well as attend the convention. If there are moments between meetings, or perhaps enroute home, when this June issue profitably occupies your interest, the editors and staff will be well rewarded.

CALIFORNIA MEDICINE, it should also be noted, has made another and much greater gift not only to the physicians who may attend this convention, but to all of American medicine. Its editor for twenty-one years has resigned that post and he is missed. He will be inaugurated the 123rd President of the American Medical Association at this meeting in San Francisco.

We wish the AMA a happy and productive convention and Dwight L. Wilbur particular Godspeed as he assumes his enormous responsibility.

A New Kind of Forum

A NEW KIND of forum is inaugurated elsewhere in this issue. It is a forum with a practical purpose which goes beyond the usual exchange of views, and sometimes emotion, which all too often leads to little or nothing except occasionally a feeling of relief or satisfaction on the part of some of the participants. The purpose of the forum on "The Scope and Responsibility of Medicine" (page 405) is to provide a means of relatively free discussion of a topic which badly needs discussion, within a framework which is not sharply restricted as to time, place or participants, and which is capable of producing an end product distilled from the discussion which might achieve formal acceptance and so be useful.

The scope and responsibility of medicine in present day society is such a topic. Until this can be identified and at least somewhat defined, it is unlikely if not impossible that rational or meaningful programming for any aspect of health education or health care can take place. The problem is first to bring interested and informed opinion to bear, provide for interaction and exchange, and then identify the threads which run through the discussion, and eventually try to weave them into some sort of fabric which will receive general approval and acceptance. It is only when a problem is well defined and a clear question is asked that a correct answer can be found.

If the forum on "The Scope and Responsibility of Medicine" can achieve its purpose it will also demonstrate the usefulness of a new technique in the decision making process within a democratic human institution. This could be its greatest contribution.

Current Knowledge of Psoriasis

ANY DISEASE WHICH may affect between 200,000 and 600,000 persons in the United States is an important one. Although psoriasis is considered benign in the sense that it is not significant as a cause of death, it most certainly is not benign in the socio-economic sense. An old synonym, *lepra alphos,* apparently stems from biblical times when psoriasis probably was frequently mistaken for leprosy. In any event, psoriasis is a dread, loathsome disease which, in the words of Sulzberger, more frequently ruins the reputation of the dermatologist than any other dermatosis, with the possible exception of warts. It is quite unpredictable and capricious, and the tendency is life-long.

Elsewhere in this issue is a superlative review of current knowledge of psoriasis by Farber and McClintock. It is a testimonial to the productivity of the broadly based research program at Stanford Medical School. Such an article cannot be encyclopedic (several hundred articles and monographs are published on the subject each year), but it does contain a balanced and critical summary of the pertinent information now available concerning this important disease.

The review accurately reflects that we have no startling new facts about psoriasis. It has been known for a long time, on the basis of excellent studies in Germany, Denmark and this country, that the disease has strong genetic overtones, and it is well established that psoriasis consists of an increased epidermopoiesis. Curiously, the only noncutaneous component thus far described is psoriatic arthritis, unless one includes Reiter's syndrome as being a variant of psoriasis. It is a disease, however, in which there may be systemic repercussions, as for example the hypervolemia and increased cardiac output which may complicate generalized erythroderma and exfoliation, even leading to cardiac decompensation.

Drs. Farber and McClintock tell us of newer understanding of traditional topical treatments (including the dangers thereof) and point out that the use of topical corticosteroids is not without hazard. As for systemic treatment, the beneficial effect of inorganic arsenic has been recognized for at least a century, coupled with awareness of serious drawbacks, principally the delayed onset of malignant change. Systemic corticosteroids have a place occasionally in the treatment of severe psoriasis but must be employed with critical judgment and control. Methotrexate and other chemotherapeutic agents developed for the management of malignant disease may be of aid in highly selected cases as suppressive, non-specific therapy.

The authors point out that no explanation for the pathogenesis of psoriasis is as yet at hand. The possibility of an enzyme defect is appealing in this era of molecular diseases, but no substantial information exists in support of this. Even if the genetic pattern were more clearly delineated, there is as yet no particular metabolic pathway which can be implicated.

Farber and his colleagues have made a significant contribution in characterizing the disease more clearly and in assessing and evaluating its natural history. The etiology and pathogenesis of psoriasis still elude us. While this remains true, therapy will continue to be empirical.

Routine Chemical Screening

IN RECENT YEARS routine screening for asymptomatic disease has assumed a prominent role in the

practice of medicine. Technological developments such as the multichannel laboratory analyzer and electronic data processing have made it feasible to measure many physiological and chemical parameters routinely on large numbers of apparently healthy persons, rather than to reserve laboratory tests for persons with suspected clinical disease. At the same time, routine screening has evoked considerable discussion as to its merits.

The hope, of course, is that the serious chronic diseases are more amenable to definitive therapy if detected early, and that complications will be prevented by early diagnosis and treatment. While several studies of the long term effects of routine screenings are under way here and abroad, it remains appropriate to examine the more immediate effect of screening and to point out the problems that must be solved through further research.

Elsewhere in this issue of CALIFORNIA MEDICINE, Schoen presents a review of some of the difficulties associated with routinely measuring clinical chemical factors. The article emphasizes the great need to define the normal biochemical state—a need that existed before the advent of mass screening but has been accentuated by performing tests on large numbers of healthy persons. Since different clinics use widely different definitions of normal, comparisons of the proportions who are abnormal have little meaning, and surely "more sick" cannot be equated to more abnormal. Normal ranges must be developed that take into account age, sex, geography and other variables, such as drug usage, that affect the test, if the physician is to make intelligent decisions. It is to be hoped that the future will see other approaches to the concept of normality such as Williams',[1] which is based on a profile of tests that are integrated and compared with previous tests on the same patient.

A related problem is that many tests have only recently been done routinely, and much research is needed as to the clinical significance of abnormal results. Schoen appropriately points out that 70 percent of significant unsolicited abnormal findings are revealed by testing blood glucose and urea. This is to be expected because physicians have had enough experience with these tests to appreciate their clinical usefulness. Similar long-term experience must accumulate before the usefulness of other, newer tests can be evaluated.

The lack of specificity of screening tests results in a large number of false positives and may add to the burden on already overtaxed medical resources, as well as cause undue anxiety to the patient. It is well to reiterate that screening tests are performed on a mass basis to distinguish between persons likely to be healthy and those likely to be sick, and that, used as such, they are not diagnostic tests. One reason for lack of specificity, implied by the article but deserving of special emphasis, is poor quality control. Asserting that a 25 to 75 percent variability can occur with poorly controlled automated equipment, Williams[1] pointed out that automation imposes an even greater responsibility for the clinical pathologist. Automation does provide the opportunity, however, to establish more effective quality control programs.

The development of automated determination of clinical chemical factors has, on the other hand, provided the potential of learning a great deal about the prevention of disease. It is now possible to monitor many biochemical processes in large numbers of persons, repeatedly over time, with good accuracy and at relatively low cost. If, as Schoen suggests, additional channels do not at present provide significant information, the solution is not to abandon their use but to study how this increased power of measurement can be applied for the benefit of the patient.

[1]Williams, G. Z.: Effects of automation on laboratory diagnosis, Calif. Med., 108:43-45, Jan. 1968.

A Biologic Society in an Age of Science

THE PREMISE that scientific progress is the most significant cultural force in today's world is acceptable to almost everyone. This force finds expression in the new complicated technologies of an ever more complex technologic society which now requires more scientific education, greater specialization and increasing interdependence among those human beings who must live in, adapt to and operate this scientific and technologically complex society. It therefore seems likely, if not inevitable, that as more science is taught in schools, and as more science is required in daily living, the approach and methodology of science will gradually become the matrix or framework of cultural thought. As this occurs, whatever is unscientific dogma or doc-

trinaire belief or prejudice will first be questioned and then subjected to trial by experiment. If found wanting it will be exposed and expunged. This has been occurring in scientific medicine and is beginning to happen in society. The impact of this is certain to be far-reaching.

Just as science established the biologic nature of man during the last century, so it is certain to establish the essentially biologic character of human society, probably in this. Human society and human institutions are composed of human beings and it will be shown that they are in a very real sense extensions of biologic human nature. When this occurs a biologic society and its human institutions will be examined in terms of biologic principles and in terms of their health and fitness to survive and to cope with a changing and often hostile environment.

If it is true that an increasingly complex technologic society will develop a scientific approach and methodology as the ground substance of its social and cultural thought, and if it can be shown that human institutions and human society are fundamentally biologic in nature as are the human beings from which they spring, then there will promptly be needed a scientist who is also a practitioner of this new human biology.

This scientist-practitioner of the new human biology should have at his command an authoritative body of knowledge concerning the health and health care of patients, human institutions, and even the body politic. In each instance of trouble he will hear the presenting complaint, study the present illness, and review past history, family history and social history for any pertinent information. He will examine the problem and do whatever research is necessary in the form of studies or tests. He will reach a diagnosis, the validity of which he will test in treatment, always striving to do no harm in therapy. In deciding upon the course of action this scientist-practitioner will bring to bear his knowledge and skills, balance scientific, humanitarian and economic values, and secure the understanding and cooperation of whomever he must work with to carry out the treatment which he advocates. Finally he will evaluate the result and add this information to his experience and perhaps even to the scientific literature.

It is suggested that we are now in fact on the threshold of recognizing the biologic nature of human society in an age of science and the need for a scientist-practitioner of this new human biology. It is further suggested that this would be a natural extension of the traditional role of the physician and that organized medicine can be an instrument to hasten the advent of a biologic society in a scientific age and to promote the art and science of medicine within the framework of this new human biology.

Incredible

In its critique of a section in the President's Health Message to the Congress on 4 March 1968, the Bureau of Research and Planning of the California Medical Association calls attention to what appears to be an inappropriate use of statistical data in predicting increases in physicians' fees during the period 1965 to 1975. According to the Bureau report (see page 480) government statisticians have added anticipated increases in the use of services rendered by physicians to an expected increase in the prices for these services in predicting that physicians' fees will rise by no less than 160 percent during this ten-year period. While it is to be expected that *prices* for physician services—that is, fees—will rise in response to increases in the cost of living, inflation and other factors, the predicted greater *use* of those services ought not be considered a factor so far as fees are concerned. The total cost for increased amounts of services is one thing, fees quite another.

Incredible as it may be, that part of the President's message seems truly incredible.

California Medical Association

Regional Medical Programs

Report of the California Committee on Regional Medical Programs to the meeting of the Council of the CMA, 4 May 1968.

On April 1 and 2 a site review team from the Division of Regional Medical Programs came to San Francisco for the purpose of examining the applications for operational programs in heart disease, cancer and stroke, submitted to the National Advisory Council by the California Committee on Regional Medical Programs.

The review team, during its full two-day site visit, examined all operational grant applications thus far submitted by the California Committee, that is both the December 1967 proposals, and those approved for submission in March of this year.

The 14 operational proposals submitted in December requested $12,213,966 in long range support. The March package of five proposals sought $2,649,920. Two additional requests were included in the March submission. These sought funds specifically earmarked by Congress for categories outside the usual channels of funding through the Division of Regional Medical Programs. The total for the two earmarked fund proposals is $1,942,544.

Brief descriptions of the proposals submitted in December:

- The single topic generating the most interest dealt with the training of personnel for and the equipping of coronary care units. Four proposals were submitted, from the University of California San Francisco Medical Center, University of Southern California and UCLA. Each differed in some detail from the others as each sought to meet with individuality the needs expressed in the local communities.
- For the Watts-Willowbrook area of Los Angeles a proposal to help establish a postgraduate medical school was put forth jointly by USC and UCLA. Internship and residency programs would be created, along with a broad and continuing program of postgraduate education for physicians, nurses and related health professionals.
- In Roseville the UC Davis School of Medicine would help local practitioners turn their community into a "living laboratory," testing innovative diagnostic and treatment modalities, setting up physician and paramedical training programs for heart disease, cancer and stroke.
- The California Heart Association would expand its highly successful cardiovascular student research program.
- UCLA would provide training in angiographic techniques in a two-part program, one for 24 radiologists each year over a three-year span, providing them with two-months concentrated training. The other would offer a full year of advanced training for 16 radiologists.
- UCLA would expand its medical television

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network offerings to other institutions both within and outside of California.

- UCLA and UC Davis both would provide mobile videotape recorders for hospital staffs in the San Joaquin and Sacramento Valleys, offering teaching tapes, cameras and playback units to study teaching and demonstration techniques carried on in the local hospital. The units would be trucked from one hospital to the next on pre-set schedules.
- UCLA would develop learning and instruction languages and programs for a medical computer.
- Loma Linda University School of Medicine proposes to offer increased and expanded library services to practicing physicians throughout its area.
- Loma Linda would also conduct a one-year demonstration of the feasibility of remote computer display terminals for EKG, cardiac output and other physiologic signs. A physician 200 miles from the computer could hook his patient to the remote terminal, pick up his telephone, dial the computer and ask it to compare the patient's symptoms with normal ranges. The computer reading would be checked for acceptability, in each case, by a cardiologist.

The operational proposals submitted in March:

- The San Francisco Medical Center proposes a network of northern California hospitals to establish new or provide improved clinical diagnosis, treatment, social service and consultation for cancer patients. The two-part program would also create or enhance radiological physics and nuclear medicine capabilities.
- UCSF would establish, through its Division of Ambulatory and Community Medicine, a coordinated year-round general practice residency program in cooperation with Sonoma Community Hospital.
- A pilot training program to explore the kinds of special skills needed or desired for physicians in intensive care units in small general hospitals is proposed through the UCSF planning office.
- UCLA proposes to establish a medical library service network, linking major hospitals in its service area.

The two earmarked fund proposals come from the University of California at Irvine and the San Francisco Medical Center.

- UCI proposes an Orange County-wide training and demonstration program for pediatric pulmonary disorders. Diagnosis, treatment, rehabilitation and social adjustment for chronic pulmonary diseases is included.
- The UCSF proposal would integrate and augment an existing hypertension program, extending improved diagnosis and management of hypertensive patients, including demonstration programs for referral and follow-up, throughout Area I.

The first year costs for all proposals submitted, if approved as requested, total $4,942,649. Most of the proposals would run for three years; some pilot and demonstration projects, however, would expire after one year, and a few would extend to five years. The total long range costs requested are $16,806,430.

The National Advisory Council site review team showed great interest in these 21 proposals. The Council is expected to announce its action on them about mid-June.

Estimates of Physicians' Fees in The President's Health Message

A critique of a section in the President's health message to the Congress dated 4 March 1968, prepared by the CMA Bureau of Research and Planning

AT A TIME WHEN considerable public and legislative discussion centers around the costs of health care, and at a time when the onus for the rising costs of such care is being placed by numerous persons primarily upon the physician, it is both unfortunate and regrettable to observe what we consider to be the misuse and inappropriate use of data by the Executive branch of government to further misconceptions about the increases in physicians' fees. A glaring example of this is to be found in the section of the President's Message of 4 March to the U.S. Congress, under the caption of "Controlling Costs of Health Care." The erroneous impression which can be, and has already been, gained is that physicians' fees will have increased 160 percent in the ten-year period from 1965 to 1975. Such a mis-impression can result from the fact that the President's Message deals with two separate and distinct sets of estimates—each of which is derived from a separate base.

(1) In referring to the fact that "the cost of living will increase by more than 20 percent by the end of 1975, the President's message is predicating the rise in the CPI on an increase of approximately 2 percent a year. Recent indications are that the Consumer Price Index is increasing at the rate of between 3.0 percent and 3.5 percent per year. Therefore, by the end of 1975, the increase over the decade may well be closer to, or exceed, 30 percent.

(2) The more serious fault in the presentation of the data, however, lies in the manner in which the increase in physicians' charges is presented. The statement that "doctors' bills will climb 160 percent" is a composite of increases in fee levels *and* increases in consumption. The best estimate based on recent trends in fees is that levels will increase approximately 60 percent (or less) in the ten-year period; the remainder of this projected 160 percent increase must necessarily be attributable to an increase in the *amount* of services consumed. In any event, the figure which would be comparable to the projected 20 percent increase in consumer prices would be 60 percent *not* 160. It is likely that if a figure for all goods and services had been developed which would have been comparable to the 160 percent increase for physicians' services, there would be even less disparity between the two projections. Therefore, although the statistics employed may have validity standing by themselves, they are misleading because they contain a "mix" of percentages (a) based upon the Consumer Price Index, and (b) based upon *projected expenditures* for medical care, including physicians' services. The casual reader of the Message, or the average interpreter, is therefore likely to draw improper conclusions from the sequence of the data used. That such unwarranted conclusions can be drawn is already evidenced by the numerous reports in the public press which, unfortunately, has accepted the data at face value.

One further observation: the President's message refers to the "cost of living." This term, too, is incorrect inasmuch as the Consumer Price Index is *not* a cost of living index. Although the Bureau of Labor Statistics has been careful to avoid use of the term "cost of living," it is curious to find this expression employed in an important message to the Congress.

The Bureau of Research and Planning can only comment, with dismay, that in juxtaposing two sets of estimates which are derived from different bases or assumptions, and in using other language of questionable appropriateness, the "credibility gap" relating to physicians' fees has been widened by a wide margin.

The Bureau's hope is that this critique and explanation will enable physicians to inform themselves and others of the facts, including the proper interpretation of the data in the President's Health Message.

New Legislation Proposed to Lighten Malpractice Burden

WITH PROFESSIONAL LIABILITY PREMIUM RATES soaring to heights undreamed of ten, or even five year ago, the CMA is painfully aware of the burden its members are required to bear in order to secure professional liability insurance.

As in the past, the CMA, under the direction of the Medical Review and Advisory Committee, continues to initiate multi-pronged assaults on the myriad problems which are enveloping the provision of physician malpractice insurance. And, a vital part of CMA's action program to improve the "professional liability atmosphere" is the sponsorship of six new bills which have been presented to the current California Legislature.

They are:

- A.B. 574 (Deddeh, Chula Vista), which would provide for a separate trial of the defense of the statute of limitations before any other issue in the case can be tried, upon motion of either party.
- A.B. 1068 (Veysey, Brawley), which would place upon the plaintiff the burden of proving the defendant's negligence, and would establish that injury alone does not constitute either the presumption or inference of negligence.
- A.B. 1069 (Veysey, Brawley), which would extend the present concept of privileged communications to the proceedings and/or records of medical review committees of local medical societies and hospital staffs.
- A.B. 1070 (Veysey, Brawley), would require the plaintiff to file a nominal fee ($500 cost bond) to discourage the filing of nuisance suits.
- A.B. 1071 (Veysey, Brawley), which would

require that the time limit for commencement of an action against a physician begin with the date of the alleged wrongful act unless fraud or intentional concealment is proven.

• A.B. 1270 (Wilson, San Diego), which would provide that any advance payment by an insurance carrier to an injured party could not be construed as an admission of liability.

In addition to the above, CMA presently contemplates submitting future legislative proposals which would:

(1) Set reasonable limits for damages under personal injury awards to insure that premium rates for this type of coverage will not become prohibitive; and,

(2) Set some boundaries on the doctrine of "informed consent."

California physicians can assist CMA by informing their local State legislators of the serious nature of the malpractice problem and its potentially grave and unfavorable effects upon the provision of health care in California.

Council Highlights

Highlights of the Actions of the California Medical Association Council Meetings, February 23 to 24, 1968, Los Angeles and March 22 to 28, 1968, San Francisco

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.

541st Meeting, February 23 to 24, 1968. Los Angeles

CMA Mental Health Committee survey of the state's 14 mental institutions was approved for transmittal in summary report form to the state administration.

Medi-Cal developments were discussed and the Council voted approval of a pre-payment risk assumption arrangement plan with the state through California Blue Shield for physicians' services. The Council also voted approval of the recommendation of inclusion of a co-insurance feature for the group II medical indigents beneficiaries under the Medi-Cal program. In addition, the Council voted to oppose the concept of individual negotiated fee schedules under Medi-Cal, and the Council reaffirmed CMA support of "usual, customary, or reasonable fees."

CMA Annual Session meeting dates were considered and the Council voted to submit a resolution to the House of Delegates establishing CMA's Annual Meeting to be held between 1 February and 15 March of each year.

Award of recognition to Dr. Edwin H. Lennette for outstanding work in virus research was approved for presentation at the CMA's 1968 Annual Session.

CMA Organizational Review and Planning Committee report was approved requesting the Scientific Board to establish an inter-specialty subcommittee charged with continuing efforts to maintain and to improve CMA-specialty and inter-specialty coordination and cooperation.

Communications' Sub-Committee on Component County Society Officers Conference; Roles and Objectives of the Commission; and the Commission on Communications' budget were approved by Council. Also approved was a TV series to be carried by KGO-TV, San Francisco, (Channel 7), in conjunction with the CMA.

New CALPAC chairman Dr. James C. MacLaggan was appointed to succeed outgoing chairman Dr. Malcolm C. Todd.

Legislative matters were considered as follows: Voted to oppose AB 155 and SB 74 which authorized counties to produce and sell raw milk; approved a second annual spring CMA officers visit with California legislators in Washington, D. C., in cooperation with California Blue Shield; voted to proceed with professional liability legislation as earlier approved; and voted to study SB 53, a bill dealing with professional corporations, for report at the next Council meeting.

AMA-ERF funds for distribution to medical schools in California were approved on the basis of a new formula between state endowed schools and privately endowed schools.

542nd Meeting, March 22 to 27, 1968, San Francisco

Council approved a set of recommendations on ethical and legal implications of **organ transplants.** They are:

- The diagnosis of death must be made by physicians with skill and judgment. No new laws or rigid criteria are needed, nor would they even be helpful, and might be harmful.
- The medical staff of each institution performing organ transplants should create a committee responsible for setting guidelines and supervising transplant research in the institution. The guidelines should correspond to already defined ethical rules governing research, and to research developments.
- To avoid even unconscious bias, the physician or physicians for the donor, and the physician or physicians for the recipient should be separate and independent.
- There should be changes in current consent laws.
- The many groups who are active in making pronouncements and statements should confer with each other so that the public and legislators are not given conflicting and confusing information.

A special issue of CALIFORNIA MEDICINE to be published for distribution at the AMA June convention in San Francisco was given approval. This will be one of a series of steps being taken to gain national recognition for the scientific journal.

The Role of Medicine in Society, Part II of the Fourth Progress Report, "A Role for Medicine in a New Era of Health Care," will be transmitted to the editor of CALIFORNIA MEDICINE for publication. [It was published in the May issue.]

A plan for **Medi-Cal utilization review in hospitals** was approved. Representative review panels, each consisting of an equal number of physicians and hospital administrative personnel, will be established by CMA and the California Hospital Association. Physician members will review the medical aspects and hospital administrative personnel will review administrative matters. The panels will have the authority to recommend termination of Medi-Cal payments to individual hospitals that do not comply with accepted standards of care. County medical societies will be involved in appointments to the representative review panels. The entire program will be a cooperative effort by the administrator of the state Health and Welfare Agency, contract carriers, CMA and CHA.

The **professional corporations act** (S.B. 53) now before the California Senate was approved by the Council.

Efforts by departments within the state administration to initiate their own **regional health planning** programs will be opposed, and these departments will be urged to coordinate their planning through the State Health Planning Council.

A statement on **mandatory clinical laboratory proficiency testing** was given Council approval. The statement says that "after licensing by the state, the imposition of a program by government to require further proof of competency by physician-directed clinical laboratories is unwarranted, and therefore the CMA does not support mandatory proficiency testing by a government agency." It does confirm CMA support of voluntary proficiency testing of all licensed medical laboratories, however, and suggests that, when possible, proficiency testing be a requirement for membership in specialty organizations.

A statement on the **CMA Appeals Committee,** defining its areas of responsibility, make-up and operating procedures, was approved.

Recently introduced bills to improve the **professional liability** atmosphere in California were reviewed by CMA Legal Counsel Howard Hassard.

543rd Meeting, March 28, 1968, San Francisco

The Council elected its officers, made its administrative appointments, reviewed and made committee appointments, discussed CMA's subsidiary organizations, passed bank resolutions, and set the next meeting of Council for May 3-4, 1968, Sacramento.

In Memoriam

Blumenfeld, Edward Alexander, Los Angeles. Died 23 April 1968 in Los Angeles of acute coronary thrombosis, aged 68. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1924. Licensed in California in 1952. Doctor Blumenfeld was a member of the Los Angeles County Medical Association.

✣

Brown, J. Scott, Santa Barbara. Died 25 April 1968 in El Cerrito, aged 92. Graduate of the University of Illinois College of Medicine, Chicago, Illinois, 1902. Licensed in California in 1912. Doctor Brown was a member of the Los Angeles County Medical Association.

✣

Byron, Francis Randolph X., Pasadena. Died 27 April 1968, aged 55. Graduate of the University of Nebraska College of Medicine, Omaha, Nebraska, 1936. Licensed in California in 1948. Doctor Byron was a member of the Los Angeles County Medical Association.

✣

Coleman, William Pinchot, North Hollywood. Died 13 April 1968 in Los Angeles of coronary thrombosis, aged 59. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1936. Licensed in California in 1936. M.D. degree from California College of Medicine, 1962. Doctor Coleman was a member of the Los Angeles County Medical Association.

✣

Comer, Bartholomew Joseph, San Diego. Died 25 April 1968 of cancer, aged 50. Graduate of Georgetown University School of Medicine, Washington, D. C., 1942. Licensed in California in 1949. Doctor Comer was a member of the San Diego County Medical Association.

✣

Dement, John Carey, Berkeley. Died 7 April 1968 in Kensington, aged 72. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1921. Licensed in California in 1921. Doctor Dement was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Etter, Omer R., Alameda. Died 18 April 1968 of cerebral hemorrhage, aged 77. Graduate of Jefferson Medical College, Philadelphia, Pennsylvania, 1917. Licensed in California in 1923. Doctor Etter was a member of the Alameda-Contra Costa Medical Association.

✣

Fairbairn, Gerald Ford, Belmont. Died 20 April 1968 in Redwood City, aged 72. Graduate of Queen's University Faculty of Medicine, Kingston, Ontario, Canada, 1922. Licensed in California in 1935. Doctor Fairbairn was a member of the San Mateo County Medical Society.

✣

Folte, Arno Gustav, San Francisco. Died 17 February 1968 in San Francisco of massive cerebral thrombosis, aged 77. Graduate of College of Physicians and Surgeons, San Francisco, California, 1918. Licensed in California in 1918. Doctor Folte was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Foster, Percy A., Los Angeles. Died 12 April 1968 in Los Angeles of pneumonia, aged 78. Graduate of the College of Physicians and Surgeons, Los Angeles, 1915. Licensed in California in 1915. Doctor Foster was a member of the Los Angeles County Medical Association.

✣

Harper, Walter Henry (W. Henry), San Jose. Died 3 April 1968 in San Jose of heart disease, aged 50. Graduate of Harvard Medical School, Boston, Massachusetts, 1943. Licensed in California in 1949. Doctor Harper was a member of the Santa Clara County Medical Society.

✣

Perry, Daniel J., Santa Monica. Died 3 April 1968 in Santa Monica of generalized motor neuron disease, aged 50. Graduate of University of Cincinnati College of Medicine, 1942. Licensed in California in 1947. Doctor Perry was a member of the Los Angeles County Medical Association.

✣

Phelps, Lucius Belding, La Habra. Died 16 April 1968, aged 90. Graduate of Chicago College of Medicine and Surgery, Illinois, 1907. Licensed in California in 1931. Doctor Phelps was a retired member of the Orange County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Vini-Coff, Alan Ross, Berkeley. Died 21 March 1968 in Berkeley, aged 46. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1945. Licensed in California in 1945. Doctor Vini-Coff was a member of the Alameda-Contra Costa Medical Association.

✣

Weisman, Frederick L., Northridge. Died 8 April 1968 in Granada Hills of transitional cell carcinoma, aged 39. Graduate of University of Michigan Medical School, Ann Arbor, 1954. Licensed in California in 1959. Doctor Weisman was a member of the Los Angeles County Medical Association.

LETTERS *to the Editor*

Carpal Tunnel Syndrome

To the Editor: Doctors Doyle and Carroll in Volume 108, No. 4 very well cover the carpal tunnel syndrome, bring it to the attention of some still unaware of the entity, and present details of pathogenesis and etiology which are of interest to those who practice surgery of the hand as an implement of the adjacent extremity.

The editorial "Nerve Entrapment in the Upper Extremity" beautifully complements their essay and points out the obvious fact that nerve compression, or irritation, from the cervical cord distally, must be fully considered prior to a firm diagnosis of carpal tunnel syndrome.

The purpose of my letter relates to one phase of the matter which is mentioned under Conservative Treatment in the paper of Doctors Doyle and Carroll.

A steroid suspension may be injected without harm, and often with curative effect, in many locations. One who performs extremity surgery often sees the chalk-like plaques which are the residue of these injections. Apparently the material does little or no damage in tendons, tendon sheaths, bursae and ganglions.

This is not true in a nerve trunk. The residual steroid material is a foreign body and must interrupt continuity of neurofibrils if introduced into a nerve, very likely in greater degree than the underlying compression within the carpal tunnel.

This has long concerned me, and I do not think that even the most experienced can with certainty inject hydrocortisone into the carpal tunnel around but not into the median nerve, and I strongly feel that this approach to management of the carpal tunnel syndrome should be abandoned.

This opinion is emphasized by a case currently under my care. The patient, a 50 year old woman, developed right wrist pain and paresthesias over the median distribution attributed to repetitious use of the member at her work. She was seen in an adjacent medical facility and was given injections of "cortisone" into the wrist on three occasions but without relief.

Two months or so later she was referred to a competent orthopedist. An electromyogram was done, and she was given an injection of "cortisone" into the wrist, again without benefit.

The diagnosis of advanced median nerve alteration within the carpal tunnel was quite evident at the time that I first saw her. There was hypoesthesia over the median distribution and an "electric" feeling on pressure over the carpal tunnel. There was pronounced atrophy of the thenar eminence. Exploration of the median nerve, with unroofing of the carpal tunnel, was strongly indicated.

Dissection showed the presence of chalky white material entirely within the sheath of the nerve and apparently occupying 50 percent or more of the nerve trunk. There was no means of removing this other than by resection of the nerve, and this did not seem warranted at the time of surgery.

Three months following operation the patient has improved somewhat, but it is obvious that a good result will not be obtained, and one wonders if resection and anastomosis of the infiltrated segment of the nerve would not have been a better approach.

ROBERT J. MOES, M.D.
1930 Wilshire Blvd.
Los Angeles, Calif. 90057

Dissent

To the Editor: Please allow me to express my disagreement and disapproval of the editorial "The Baby and the Bath Water," Cal. Med., April 1968. The basic tenet on which Medi-Cal is founded is

the right (?) of all to receive medical care of equal quality, regardless of the ability to pay for such care. This makes no more sense than to propose all children need a quality diet and, therefore, have the public trough provide steak and eggs for all.

If we believe in the American system, we should extend charity to those in need and not ask the state to foot the bill. We should, indeed, "throw the baby out with the bath water," if this means nonparticipation in a system that invites fraud, deception and outright dishonesty.

FRED L. GREER, M.D.
Whittier, California

Student Loan Fund

To the Editor: Enclosed [following] is a letter in reply to an inquiry regarding the status of the [American Medical Association] student loan fund, of which I have felt, and continue to feel has been an excellent program for physician contribution. In this way an unmet need has been completed.

The tenor of the reply indicates the nature of the inquiry and I thought the reply a most interesting one and an excellent record of both help and recovery. I am forwarding a copy of the letter to you, insofar as you might like to insert this as an item of interest in CALIFORNIA MEDICINE to further encourage contributions by California physicians. I thank you in advance for your courtesy.

ROBERT L. GARRETT, M.D.
Vallejo, California

DEAR DOCTOR GARRETT:

Your letter to Doctor Blasingame dated March 27 in re the Student Loan Guarantee Program has been referred to me for answering. We appreciate your inquiry, and I am glad to provide you information about the status of pay out of loans.

The October 25, 1967 Report to the Board of Directors of AMA-ERF showed that we had 25,189 open interim notes, that is, active loans by medical students, interns and residents which were not yet in pay out status. At that time, we had 3,729 notes that were in pay out status. Of this number, 144 were delinquent.

32 deaths	17 military
38 slow payment	7 health
20 drop outs	12 other
18 bankruptcies	

On a gross figure basis, this would indicate under 4% of borrowers, who were in pay out status, were delinquent. However, recovery from estates in the case of death, eventual payment by those who are slow payers or drop outs, anticipated repayment by those in military, show us in a position where we will have a very small net loss.

I think you will see by this that our experience in the program has been and continues to be very good.

RICHARD M. NELSON
Director, Program Development
American Medical Association

THUMB OPHTHALMODYNAMOMETRY

"You always carry an ophthalmoscope, but you don't always carry an ophthalmodynamometer. If you are doing ophthalmoscopy in patients with fairly severe disease, just press in a bit with the thumb holding up the upper lid. If you see that artery begin to wink at you, you had better suspect that you will have a low ophthalmodynamometer reading."

—DAVID L. KNOX, M.D., Baltimore
Audio-Digest *Ophthalmology,* Vol. 6, No. 6

PUBLIC HEALTH REPORT

Acting Director, State Department of Public Health
Hamlet C. Pulley, M.D., M.P.H.

The Deadly Din

NOISE IS UNWANTED and intrusive sound. Technological progress brings with it an ever-increasing environmental cacophony and noise has become not just an adjunct, but a permanent part of modern man's life. As such, it constitutes one of the chief drawbacks to the enjoyment of urban living. We have long recognized that noise is both an occupational hazard and a public nuisance. Has urban noise now reached intensities which pose a danger to community mental or physical health? There are indications that it has. Noise has become another environmental pollutant.

For California industry, programs to conserve the hearing of employes are recommended when daily exposure to sound levels continuously for over five hours exceeds 85 decibels in the principal speech frequencies; and they are mandatory when the level goes above 95 decibels. It must be added that even the lower limit will not prevent hearing impairment in hypersusceptible persons. Yet some urban noise intensities currently approach or exceed these occupational damage-risk criteria. The situation becomes more ominous in light of a report that urban sound levels in the United States are increasing by one decibel per year.

Sound pollution has grown *pari passu* with air pollution. Especially in California's major metropolitan areas, this side-by-side growth is no coincidence. Here, the major source of air and sound pollution stems from the internal combustion and related types of engines, machinery and equipment: Jet and propeller aircraft, automobiles, buses, motorcycles, trucks and the like are producers of both air and sound pollutants. Other sources of community noise are public entertainment and amusement places; electric substations and air-conditioning systems; radio and television sets, and electrical-mechanical household appliances; percussion and other musical instruments, especially those electronically amplified. Additional major sources are horns and sirens; mechanized industrial operations and construction, repair and demolition equipment.

The effects of occupational overexposure to sound are well known. Chronic industrial overexposure produces permanent hearing loss. In addition, an explosion's momentary intensive impulse noise can damage ear structures and cause deafness. At the larger community level, excessive noise affects sleep and efficiency, interferes with speech and communication, and causes fatigue. Noise constitutes a source of annoyance and complaint—especially if it is considered unnecessary. Extreme loudness, however, is not an essential component of disturbing sounds. The interpretation of and reaction to noise are highly subjective. In fact, one man's music is another man's noise.

Noise stress can produce uncontrollable physiological strain in affected persons. Vasoconstriction, skin blanching and muscular contraction occur, together with sudden hormonal discharge which further increases tension and anxiety. In turn, cardiovascular, neurological and other system functions are affected. Recent otological studies indicate that the louder the environmental sound levels, the earlier and more pronounced the onset of presbycusis. The psychological effects of noise are equally important, especially to per-

sons with debilitating, chronic physical or emotional disorders. In addition to overt stress reactions, noise may produce subtler psychological and physiological strains, more difficult to detect or measure — an area still needing much medical study.

Evaluations both of community noise and reaction to sound pollution are complex. Many factors must be studied at each key location: Noise characteristics, time of its occurrence or recurrence, topography, house construction standards, residential or industrial characteristics. How the community developed, its economic basis and the attitudes of its members are also factors which must be understood. These factors must then be correlated with group psychology, plus political and economic considerations.

The present lack of precise community noise criteria and standards should not be surprising, therefore. Dearth of related clinical and epidemiological studies, lack of appropriate funds and insufficient numbers of technical personnel have also retarded development of standards. Nevertheless, many communities are considering or have adopted antinoise regulations, usually based on studies done in other cities. The basic idea is excellent. Such regulations, however, must bear a direct relationship to the existing background spectrum within the specific municipality. Otherwise, they are inapplicable, unenforceable and, as a result, useless. Once more, want of technical and budgetary resources often delays solutions. There is no simple pattern fitting every community with standards for noise control.

The problem is by no means unsolvable. Many effective noise abatement measures exist and can be implemented. Zoning regulations around potential or actual noise sources can be established. For example, undeveloped areas around airports would specifically exclude land use for dwellings. Unnecessary use of vehicular horns and sirens should be curtailed. Construction, demolition and street repair equipment, industrial and office machines, household appliances and all types of internal combustion engines can be made quieter through proper engineering control systems. Governmental regulations also can be of assistance, as for example the recently established California Motor Vehicle Noise Limits, which became effective 1 January 1968.

Multiple-dwelling buildings and private homes are other areas where applicable building standards and control systems are necessary. External and internal sound controls such as the placement of trees, baffles, partitions and the use of furnishings having better acoustical insulation and other desirable properties can be employed to modify or reduce transmission of airborne or impact sounds produced by surface and aircraft traffic, footsteps, slamming doors, garbage disposal units, bathroom and other fans and the like.

The present state of acoustical science, with engineering and industrial technology, can provide effective sound control systems and devices —a costly but essential approach which will very likely require practical, reasonable governmental action. But legislation by itself will not solve the problem. To succeed, community noise abatement programs must also have massive support from industry, the medical and health professions, and especially from the public, whose health remains the prime consideration.

A noise-polluted environment produces deleterious effects on man. The imminent advent of commercial supersonic transport aircraft and related sonic booms will magnify the problem. Can the community afford to wait for possible evidence of widespread disabilities produced by excessive sound? Before the issue becomes clouded by hysteria, a reasoned, concentrated and realistic effort must be made to find solutions. Here lies a challenge to medicine and the allied professions.

NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Dr. John L. Gompertz, Oakland, was elected president of the National Tuberculosis and Respiratory Disease Association at the national meeting held in Houston late in May. Dr. Gompertz is a past president of both the California and the Alameda County Tuberculosis and Health Associations and has served on the board of directors of the national association since 1953.

LOS ANGELES

A grant of $504,253, covering a three-year period, has been awarded to the **USC School of Medicine** by the Department of Health, Education and Welfare, Public Health Service, for a study of comprehensive care in acute heart attacks.

Dr. L. Julian Haywood, associate professor of medicine and director of the four-bed coronary care unit at Los Angeles County-USC Medical Center, said that one phase of the research will be concerned with demonstrating that the specialized services available in coronary care units and their effect on patient care can improve mortality figures in a large public institution.

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The Fourteenth Postgraduate Assembly of the **Los Angeles County Society of Anesthesiologists** will be held at the Statler Hilton Hotel, Los Angeles, March 22 to 23, 1969.

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Dr. Louis Winer, Beverly Hills, was elected vice-president of the American Dermatological Association at the annual meeting at Dorado Beach, Puerto Rico, in April.

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Dr. Herbert G. Crockett of Los Angeles is the newly elected president of **Salerni Collegium,** a 1,025-member support group for the University of Southern California School of Medicine. Dr. Crockett is an associate clinical professor of surgery (neurological) at USC. **Other officers** for 1968-69 are: President-elect, Dr. Donald W. Petit of Pasadena, associate clinical professor of medicine; vice-president, Dr. Max R. Gaspar of Long Beach, clinical professor of medicine.

SAN FRANCISCO

Dr. Hibbard E. Williams, assistant professor of medicine at the University of California San Francisco Medical Center, was recently appointed a **Markle Scholar** in Academic Medicine. Dr. Williams is one of 25 young scientists in the United States and Canada to receive the five-year grant that carries an annual stipend of $6,000. He is recognized as an authority on genetic disorders relating to glucose metabolism, particularly those characterized by glycogen storage disease. He is continuing to work on hereditary diseases of children that are associated with kidney stones and liver disease.

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Dr. Herbert A. Perkins of San Francisco took office as president of the California Blood Bank System at its annual meeting in Palm Springs in April. He succeeds Dr. Robert D. Morris, Eureka, for a one-year term.

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Dr. Roberto F. Escamilla, San Francisco, was elected third vice-president of the **American College of Physicians** at the organization's recent annual meeting in Boston.

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Dr. Henry D. Moon, professor and chairman of the Department of Pathology at University of California San Francisco Medical Center, has been elected president of the American Society for Experimental Pathology.

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Dr. Bernard Diamond, San Francisco, professor of criminology and law at the University of California, recently received the **Isaac Ray Award** of the American Psychiatric Association for "outstanding contributions to an understanding between psychiatry and the law." Under terms of the award, Dr. Diamond will give a series of lectures at Cambridge University in England next fall.

SANTA CLARA

Stanford University will become sole owner of the present **Palo Alto-Stanford Hospital** 1 July under terms of a revised agreement approved by

the Palo Alto City Council. Adopted earlier by the Stanford board of trustees, the agreement will enable the university to own and operate the hospital for both community and Stanford Medical School patients. It also guarantees continued access to hospital facilities for all community physicians now on the staff.

Palo Alto-Stanford Hospital has been owned jointly by the city and the university. Palo Alto has had access to 220 beds in the main 420-bed hospital and the 150 beds in the nearby Hoover Pavilion. The city also has leased 32 acres of land from the university on which the facilities are located. The city had expressed a wish "to get out of the hospital business," and Stanford feels that a single ownership will enable its medical school to develop a **true university hospital** that is responsive to the emerging needs of medical education.

Under the terms of the agreement, Stanford will acquire Palo Alto's holdings and will operate the hospital, including the Hoover Pavilion. The university will grant **staff privileges to all community physicians** now on the hospital staff for the remainder of their professional careers. A total of 370 beds now used by patients of community physicians will continue to be available to them. Palo Alto residents will be given admisison priorities in non-emergency cases. In addition, community physicians will have access to new facilities that will be built by the medical school.

GENERAL

The California Health Data Corporation (CHD) has announced its sponsorship of a computerized health data system with a capacity to serve the more than 600 hospitals in the state. The system, known as **Medi-Record,** is designed to accept information on each patient hospitalized, to process the data at a central computer facility located in Burlingame and to provide physicians and hospital administrators with statistics on hospital operations and efficiency. At the same time, the system will create a permanent "data bank" that can be used for long range planning of health facilities, medical intelligence and medical education.

The program has the potential to **provide statistics** on incidence of disease, forms of treatment, births, causes of death, costs of hospitalization and numerous other factors affecting the approximately three million Californians hospitalized annually.

CHD is a non-profit corporation founded by the California Hospital Association and the California Medical Association. Incorporated in October 1967, it also has the support of the California State Department of Public Health.

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The sixteenth annual meeting of the **Pacific Coast Fertility Society** will be held at the El Mirador Hotel, Palm Springs, California, October 31 to November 3, 1968. Further information may be obtained from the Society's headquarters, 5410 Wilshire Boulevard, Los Angeles 90036.

The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 48 of the Advertising Section.

LIFE AFTER FIFTY—The Prostatic Age—Henry M. Weyrauch, M.D., F.A.C.S., Chief, Department of Urology, Presbyterian Medical Center, San Francisco, California. The Ward Ritchie Press, 3044 Riverside Drive, Los Angeles, Calif. (90039), 1968. 175 pages, $6.95.

The late Henry M. Weyrauch, M.D., Chief of the Department of Urology at Presbyterian Hospital and Medical Center, San Francisco, and formerly Chief of the Division of Urology at Stanford University, has left in this book, published less than a year after his death, much of the warmth and wisdom which he must have imparted to his patients.

The book is written about the man past middle age and his genito-urinary problems. But as Dr. Weyrauch points out in his preface it is written for both men and women. As he states, knowing about the prostate will lighten the task of dedicated wives and sweethearts in understanding and sympathizing with the problems of their hesitant mates and of getting them to the doctor.

The doctor, including the most sophisticated urologist, will not want to pass this book by lightly. He will find in it well thought out answers, by a man with great experience and wisdom, to nearly all of the questions and anxieties, expressed and unexpressed, relating to the urinary and sexual problems of that increasingly numerous segment of our society, men past middle age.

In a simple, non-technical, easily readable style, well larded with anecdotes and illustrated with many diagrams and amusing cartoons, the author covers the subject of the prostate gland and its problems thoroughly, beginning with his "What is it? Where is it? What does it do?" chapter through "What can go wrong? What else can happen?," and how troubles are dealt with.

After allaying fears of surgery he takes the patient reassuringly through the entire hospital and surgical routine, from "Getting ready" to "Going home." The purpose and necessity for each procedure are carefully explained in an interesting, simple but mature manner. Although some patients may later think Dr. Weyrauch was too blithe about the removal of the catheter when he says it "slips out so easily John is hardly aware that it has been done," all will agree that his information and reassurance better prepared them for their operations.

His review of the subject of "Sex after Fifty" (with and without prostatic trouble) will also give many new hope and understanding.

Dr. Weyrauch's final exposition of the cost of medical care exhibits considerable thought and research and does both the patient and doctor a service in placing these matters in proper perspective.

Mr. Ward Ritchie has admirably enhanced Dr. Weyrauch's book with his usual artistic job of design and his press has gone a bit beyond its ordinary field to produce a book of typographical excellence.

Anyone interested can be encouraged to read *Life After Fifty* with confidence that he will enjoy it and find it profitable. It is to be hoped that distribution may be expedited by the early appearance of a paperback edition.

EARL F. NATION, M.D.

* * *

DIAGNOSTIC PROCEDURES IN GASTROENTEROLOGY—With Nurse's Notes and Supplements on Instructions to Patients and Dietary Treatment — Edited by Charles H. Brown, M.D., Head, Department of Gastroenterology, Cleveland Clinic Foundation, Cleveland, Ohio. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1967. 438 pages, $19.75.

During the past several years an increasing number of sophisticated, sometimes technically difficult, but rewarding procedures have been developed by and for the practicing and academic gastroenterologist. This book is a valuable compilation of these many techniques written primarily for the Fellow studying in this field, but the book will also serve as an effective review for those previously trained and practicing gastroenterologists. There will naturally be differences of opinion regarding certain aspects of the various techniques described, but in general there is much to be gained and little lost in reviewing the experiences at this large and reputable clinic. Worthwhile additions include diet and special instructions for the patient and instructions for the nurse, although the latter are brief, "cookbookish," and certainly can not replace experience as the best teacher. The editor stresses the idea that the physician should carefully assess the necessity for any single examination in each patient to establish or confirm the clinical diagnosis—an important assessment, certainly, as some of the techniques described are done too often without forethought. A thoughtful bibliography follows each section. The photographs and illustrations are excellent especially the gastroscopic photographs taken with the Olympus gastrocamera GT-5. Of special interest are the sections on double and triple barium spray contrast studies, pancreatic scanning with selenomethionine, splanchnic arteriography, and lactose intolerance studies. The conservative conclusions regarding gastric freezing as definitive therapy for peptic ulcer are also appreciated. In conclusion this book is indeed a rewarding compilation welcomed by the student, fellow, and physician, and the price would seem to be compatible with that reward.

RICHARD J. BARTLETT, M.D.

COMMUNICATION IN SCIENCE: DOCUMENTATION AND AUTOMATION—Ciba Foundation Symposium—Edited by Anthony De Reuck and Julie Knight. Little, Brown and Company, 34 Beacon Street, Boston, Mass. (02106), 1968. 274 pages, $12.50.

Although dealing with an area of great importance to science in general, and medicine in particular, this volume will probably be of little interest to the practicing physician. In this era of the so-called "information explosion" and the deluge of the printed and spoken word, *Communication in Science* details the problem of information management, and suggests some solutions.

Following the usual colloquium format, an orderly sequence of formal papers is presented, individually succeeded by an unstructured group discussion by the symposium participants, all of whom are acknowledged authorities in various fields of scientific information management. From a general discussion of scientific communication (man-to-man, man-to-machine, and machine-to-machine) and an in-depth reviews of the current problem and philosophy of information dissemination, collation, and retrieval, the book progresses to new uses and forms of information systems, current status, and suggested future developments.

This volume will be of greatest interest to those individuals intimately involved in research activities or practice related to scientific information management and information systems, although it is generally an overview, with few new or novel concepts. Of particular reader interest, however, are discussions of information system approaches in the fields of physics and chemistry, and schemas devised to provide scientific information services on national and international bases. Sviridov's description of scientific information services in the U.S.S.R. will be of interest to even the most casual reader.

JOHN R. BELJAN, M.D.

* * *

THE HAEMOLYTIC ANAEMIAS—Congenital and Acquired—Part IV: Drug-Induced Haemolytic Anaemias, Paroxysmal Nocturnal Haemoglobinuria and Haemolytic Disease of the Newborn—Second Edition—J. V. Dacie, M.D. (Lond.), Hon. M.D. (Uppsala), F.R.C.P. (Lond.), F.R.S., Professor of Haematology, University of London (Royal Postgraduate Medical School). Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1967. 1352 pages, $11.00.

In this, the last of four volumes dealing with the topic of hemolytic anemias, the author discusses the drug induced hemolytic anemias, hemolytic disease of the newborn and the fascinating entity, paroxysmal nocturnal hemoglobinuria.

As in the previous volumes, Dr. Dacie has concisely and clearly discussed the various mechanisms of anemia associated with drug ingestion, known modes of therapy and generally reviewed current thinking about this interesting group of therapeutic "side effects." A comprehensive review of glucose-6-phosphate dehydrogenase deficiency—drug related hemolytic anemias are included.

Under the section dealing with hemolytic disease of the newborn, the clinical features, diagnostic procedures, and therapeutic measures are briefly outlined for Kernicterus, ABO blood group incompatibility, and RH hemolytic disease.

The discussion of paroxysmal hemoglobinuria is a complete and concise review of the subject.

Again, as in previous volumes, but perhaps not as frequently, the author has used illustrative case reports to advantage. Of great value to the physician called upon to treat a disease discussed here, is the exhaustive bibliography. Professor Dacie, a renowned investigator in the field of hemolysis and hemolytic anemia, has in this volume, as in the previous ones, created a reference work of monumental value to the medical profession and the busy clinician in particular.

J. EUGENE LANG, M.D.

* * *

ALIMENTARY TRACT ROENTGENOLOGY—Volumes 1 and 2—Edited by Alexander R. Margulis, M.D., Professor and Chairman, Department of Radiology, University of California, San Francisco Medical Center, San Francisco, California, and H. Joachim Burhenne, M.D., Associate Clinical Professor of Radiology, University of California School of Medicine, San Francisco; Chairman, Department of Radiology, Children's Hospital and Adult Medical Center, San Francisco, California. The C. V. Mosby Company, Publishers, 3207 Washington Blvd., St. Louis, Mo. (63103), 1967. 1203 pages, total, in volumes 1 and 2; $65.00.

The two author-editors along with 45 other authors have contributed an excellent two volume reference concerning alimentary tract roentgenology.

Some of the most outstanding European and American radiologists have made valuable contributions and physicians of all specialties concerned with problems related to gastro-intestinal tract will profit by reading these two volumes.

One criticism which may be made is that there is usually considerable overlapping of subject matter when books are written by numerous authors but this is certainly not a serious one.

Chapters on pediatric roentgenology of the gastrointestinal tract and of biliary tract in children have been added. Most often one sees such contributions only in pediatric publications.

Chapters on special procedures and on alimentary tract roentgenology from the viewpoint of an internist with a special interest in gastroenterology are valuable additions.

JUSTIN J. STEIN, M.D.

* * *

HISTORIC DERIVATIONS OF MODERN PSYCHIATRY—Edited by Iago Galdston, M.D., Chief of Psychiatric Training State of Connecticut. McGraw-Hill Book Company (The Blakiston Division), 330 West 42nd Street, New York, N.Y. (10036), 1967. 241 pages, $12.50.

Editor Galdston encloses within a flashy red and white jacket eight scholarly essays originally presented in Connecticut to a seminar on the history of psychiatry. Without the duplication inherent in many multi-author books, he succeeds in presenting a history free from "the corrupting biases of progressivism and hero worship." He does not believe that man necessarily moves from better to worse or from lower to higher. And the common man, he maintains, is as important in the shaping of history as the occasional giant. As a consequence each essay presents the history of an idea rather than a chronological account of developing psychiatry.

Derivations includes something for everyone in psychiatry. Organicists, behaviorists, psychoanalysts, as well as "community" psychiatrists will find here the historic origins of their viewpoints. Henri Ellenberger's chapter on "The Evolution of Depth Psychology" is a must for psychoanalytic candidates. Non-psychiatric physicians will profit from Philip Solomon's chapter on "Ethology, Sensory Deprivation and Overload." Physicians in state hospitals and social planners should read Alexander Leighton's concluding chapter on "Social Psychiatry." While not the only history of psychiatry for the psychiatric novitiate—perhaps not even the first for him to read—it is a worthwhile complement to existing works.

J. ELIZABETH JEFFRESS, M.D.

97th annual session program



FAIRMONT AND MARK HOPKINS HOTELS

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MARCH 23 to 27, 1968

SCIENTIFIC SESSIONS • TECHNICAL AND SCIENTIFIC EXHIBITS
MOTION PICTURE SYMPOSIA • VIDEO TAPE TV PROGRAMS
MEETINGS OF THE HOUSE OF DELEGATES

california medical association

CALIFORNIA MEDICAL ASSOCIATION



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Scientific Program

CALIFORNIA MEDICAL ASSOCIATION

Ninety-Seventh Annual Session

Fairmont and Mark Hopkins Hotels

SAN FRANCISCO
March 23 to 27
1968

HOUSE OF DELEGATES
OPENING MEETING
SATURDAY, MARCH 23
4:00 P.M.

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Information

BADGES. It is important that badges be worn at all times. Admission to scientific meetings is by badge only.

COUNCIL. The Council will meet Friday at 4 p.m., March 22, and 11 a.m. to 4 p.m., Saturday, March 23, Golden Empire Suite, Mark Hopkins Hotel.

DELEGATES. For list of delegates, meeting times, places and agenda, see pages 46 to 52.

EMERGENCY CALLS AND MESSAGES. Convention Emergency Call Number 415 781-4300 from 8:00 a.m. through 5:00 p.m., Saturday, March 23 through Wednesday, March 27.

MESSAGE CENTER (415 781-4300)—*Provided through the courtesy of the Pacific Telephone and Telegraph Company* — Registration Desk, Main Lobby, Fairmont Hotel—Registration Desk is open from 8:00 a.m. until 5:00 p.m.—The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the convention number. Routine messages will be kept at the Message Center in the Fairmont Hotel Lobby. Physicians are requested to check with the Message Center at least once a day.

TECHNICAL EXHIBITS—Grand Ballroom, Lower Level, Fairmont Tower. See pages 40 to 45.

SCIENTIFIC EXHIBITS — Grand Ballroom and Lounge, Lower Level, Fairmont Tower. See pages 37 to 38.

ORGANIZATIONAL EXHIBITS—Grand Ballroom, Lower Level, Fairmont Tower. See pages 37 to 38.

MOTION PICTURE SYMPOSIA will be shown in the Terrace Room, Fairmont Hotel. See program pages 35 to 36.

TELEVISION VIDEO-TAPE PROGRAMS will be shown in the Terrace Room. See program page 34.

REGISTRATION. Registration and information desks are located in the Main Lobby of the Fairmont Hotel. *All members, guests, and visitors are requested to register immediately upon arrival.* There is no charge for registration. Registration desks are open Saturday through Wednesday. *Admission to the general and section sessions, and exhibit area is by badge only.*

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION. (a) All M.D.'s with credentials showing that they hold valid license to practice medicine. (Membership card in C.M.A.; county medical society/association or A.M.A. membership card.) (b) Medical students will be admitted upon presentation of credentials from their medical schools identifying them as medical students. (A membership card of the Student American Medical Association or letter from their dean's office.) (c) Medical assistants will be admitted upon presentation of a letter from the physician-employer or C.M.A.A. membership card. (d) Military paramedical personnel will be admitted upon presentation of a letter requesting their admittance, written by their commanding officer. (e) Dentists (D.D.S.), doctors of veterinary medicine (D.V.M.), registered nurses (R.N.), student nurses, x-ray technicians, laboratory technicians, allied public health personnel, and others will be admitted provided they have proper identification. (f) *All questions on admission will be passed upon by a member of the Committee on Registration who will be present at the desk.*

ACKNOWLEDGMENT

PLANNING AND HOLDING an Assembly as large and as complex as the Annual Meeting of the California Medical Association requires the assistance of almost 30 program planners and 250 speakers. The Committee on Annual Scientific Assemblies appreciates their help and thanks them for all the members of the California Medical Association.

The Committee has tried to work with other medical societies and groups so that the Assembly reflects the wide interest of the California Medical Association in medical affairs. The Special Conference on Medical Manpower, cosponsored by the California Nurses Association, and the Conference on School Health are but two examples of this interest.

Last year, an important innovation was the L. Henry Garland Memorial Lecture, sponsored by the California Radiological Society. The Lecture continues and is joined this year by two additional Memorial Lectures. One is given in honor of Doctor Alice Stone Woolley by the American Medical Women's Association, and the other in honor of Doctor Charles E. Smith by the California Chapter of the American College of Chest Physicians. The California Medical Association is pleased to join these organizations in honoring Doctors Garland, Woolley, and Smith.

Committee on Scientific Assemblies
of the Scientific Board

JOHN B. DILLON, M.D., *Chairman*

Other Meetings and Entertainment

■ FRIDAY, MARCH 22

California Radiological Society Executive Board Reception—Fairmont Hotel, 20th Century Room, 6:00 p.m.

California Society of Anesthesiologists Meeting — Fairmont Hotel, Pavilion Room, 9:00 a.m. to 7:00 p.m.

■ SATURDAY, MARCH 23

CMA HOUSE OF DELEGATES OPENING SESSION—Mark Hopkins Hotel, Peacock Court—Room of the Dons, 4:00 p.m.

CALPAC Meeting — Location and time to be announced.

American College of Chest Physicians, California Chapter — Fairmont Hotel, California Room, 9:15 a.m. and 2:00 p.m. **Luncheon** — Fairmont Hotel, Crystal Room, Noon.

California Association of Medical Assistants Instructors Meeting — Fairmont Hotel, Frontier Room, 9:00 a.m.

California Medical Eye Council Meeting — Fairmont Hotel, State Room, 9:00 a.m.

California Society of Anesthesiologists — Fairmont Hotel, Pavilion Room, 9:00 a.m.

Charles E. Smith Memorial Lecture—Fairmont Hotel, Crystal Room, 1:00 p.m.

Conference on Physicians and School Superintendents —CMA Committee on School and College Health—Fairmont Hotel, Venetian Room, 9:00 a.m. and 2:00 p.m. **Luncheon Meeting** — Fairmont Hotel, Gold Room, Noon.

Conference on Smoking and Health — CMA Interagency Council on Smoking and Health—Fairmont Hotel, French Room, 9:30 a.m.

Pre-Convention Radiology Conference — Fairmont Hotel, Vanderbilt Room, 9:30 a.m.

San Francisco Dermatological Society Clinical Meeting — Room 344, Clinics Building, University of California Medical Center, 3rd and Parnassus Avenues, 2:00 p.m.

Yale Alumni Dinner — Location and time to be announced.

■ SUNDAY, MARCH 24

California Medical Assistants Association—Fairmont Hotel, Crystal Room, 9:00 a.m.

CMA Presidents' Reception honoring the Presidents of the California Medical Association and the Woman's Auxiliary — Location and time to be announced.

CMA Section on Allergy and California Society of Allergy Luncheon—Fairmont Hotel, Pavilion Room, Noon.

L. Henry Garland Memorial Lecture — Fairmont Hotel, Hunt Room, 11:00 a.m.

Stanford University School of Medicine and CMA Section on Internal Medicine—Immunology—Fairmont Hotel, Venetian Room, 9:30 a.m.

Tumor Tissue Registry/Pathology Conference—Fairmont Hotel, Gold Room, 9:00 a.m.

■ MONDAY, MARCH 25

Alice Stone Woolley Memorial Lecture — Fairmont Hotel, Crystal Room, 2:00 p.m.

American College of Obstetricians and Gynecologists, California Division, and CMA Section on Obstetrics and Gynecology Luncheon and Meeting — Mark Hopkins Hotel, Golden Empire Suite, Noon.

CMA Past-Presidents Luncheon — Fairmont Hotel, 20th Century Room, Noon.

CMA Section on Physical Medicine Luncheon—Fairmont Hotel, Garden Room, 12:15 p.m.

Stanford Alumni Breakfast—Fairmont Hotel, Crystal Room, 7:30 a.m.

University of California, Department of Medicine, and CMA Section on Internal Medicine — Endocrinology—Fairmont Hotel, French Room, 2:00 p.m.

■ TUESDAY, MARCH 26

American College of Cardiology and CMA Section on Internal Medicine — Fairmont Hotel, Venetian Room, 2:00 p.m.

CMA Delegates to AMA Meeting — Mark Hopkins Hotel, Baldwin Room, 9:00 a.m.

California Nurses Association and CMA Conference —The Nurse and Doctor Look at Problems of Manpower—Fairmont Hotel, Crystal Room, 2:00 p.m.

Component Presidents' Luncheon — Mark Hopkins Hotel, Golden Empire Room, Noon.

Symposium on Disaster—CMA Committee on Disaster Medical Care — Mark Hopkins Hotel, Peacock Court, 9:00 a.m.

■ WEDNESDAY, MARCH 27

Environmental Health Conference—CMA Committee on Environmental Health — Fairmont Hotel, California Room, 9:00 a.m.

Guest Speakers



JAMES H. CAVANAUGH



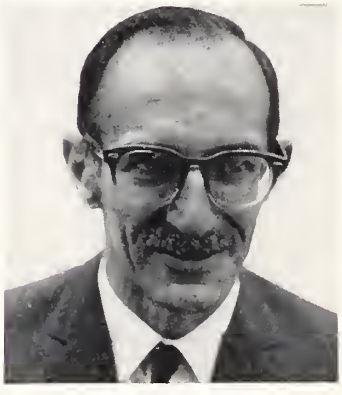
CHARLES A. CHIDSEY, III



DANIEL DEYKIN



JAMES L. GODDARD



CECIL HOUGIE



TOD H. MIKURIYA



JOHN A. OATES



EDITH L. POTTER

GUEST SPEAKERS

James H. Cavanaugh, Ph.D., Bethesda—Director, Office of Comprehensive Health Planning, Office of the Surgeon General, United States Public Health Service.

Charles A. Chidsey, III, M.D., Denver—Associate Professor of Medicine, Head, Section on Clinical Pharmacology, University of Colorado School of Medicine.

Daniel Deykin, M.D., Boston—Assistant Professor of Medicine, Harvard Medical School.

James L. Goddard, M.D., Washington, D.C.—Commissioner, Food and Drug Administration.

Cecil Hougie, M.D., Seattle—Associate Professor of Pathology, University of Washington School of Medicine.

Tod H. Mikuriya, M.D., Morrisville, Pennsylvania.

John A. Oates, M.D., Nashville—Associate Professor of Medicine and Pharmacology, Vanderbilt University School of Medicine.

Edith L. Potter, M.D., Fort Myers, Florida—Professor Emeritus, Department of Obstetrics and Gynecology, University of Chicago, Department of Pathology.

OUT-OF-STATE GUESTS OF SECTIONS AND ORGANIZATIONS

Anesthesiology

■ Henry A. Condon, F.F.A.R.C.S., London, England, Director, Department of Anaesthesiology, The Royal National Throat, Nose and Ear Hospital.

■ Thomas J. DeKornfeld, M.D., Ann Arbor, Michigan, Associate Professor, Department of Anesthesiology, University of Michigan Medical Center.

■ William F. Miller, M.D., Dallas, Texas, Professor of Medicine, University of Texas Southwestern Medical School.

■ C. Ronald Stephen, M.D., Dallas, Texas, Professor of Anesthesiology, University of Texas Southwestern Medical School.

■ Carl E. Wasmuth, M.D., Cleveland, Ohio, Department of Anesthesiology, Cleveland Clinic.

General Surgery

■ Chester B. McVay, M.D., Yankton, South Dakota, Department of Surgery, Yankton Clinic.

Pediatrics and General Practice

■ Samuel Baron, M.D., Bethesda, Maryland, Scientist, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

■ Dorothy M. Horstmann, M.D., New Haven, Connecticut, Professor of Epidemiology and Pediatrics, Yale University School of Medicine.

■ Paul D. Parkman, M.D., Bethesda, Maryland, Chief, Section of General Virology, LVI, Division of Biologics Standards, National Institutes of Health.

American College of Chest Physicians, California Chapter

■ William F. Miller, M.D., Dallas, Texas, Professor of Medicine, University of Texas Southwestern Medical School.

California Medical Television Network Television Program

■ Edwin S. Shnaidman, Ph.D., Chevy Chase, Maryland, Chief, Center for Studies of Suicide Prevention, National Institute of Mental Health.

Committee on Cancer, California Medical Association Pathology Conference

■ Walter C. Bauer, M.D., St. Louis, Missouri, Department of Pathology, Washington University School of Medicine.

■ Malcolm H. McGavarn, M.D., St. Louis, Missouri, Department of Pathology, Washington University School of Medicine.

Committee on School and College Health, California Medical Association Conference on Physicians and School Superintendents

■ Delbert Oberteuffer, Ph.D., Columbus, Ohio, Professor Emeritus, Health and Physical Education, Ohio State University.

Interagency Council on Smoking and Health, California Medical Association Conference on Smoking and Health

■ Dan Horn, Ph.D., Arlington, Virginia, National Clearinghouse for Smoking and Health.

■ Cherry Tsutsumida, M.P.H., Arlington, Virginia, National Clearinghouse for Smoking and Health.

CALIFORNIA MEDICAL ASSOCIATION ANNUAL MEETING

March 23 to 27, 1968, San Francisco

Daily Schedule of Scientific Sessions

Unless stated otherwise, all meeting rooms listed in the programs are in the Fairmont Hotel.

SATURDAY, MARCH 23 *MORNING MEETINGS*

Section Meetings:

Pathology

Special Conferences:

American College of Chest Physicians
Physicians and School Superintendents—and Noon Lunch
Smoking and Health
Radiology Cancer Conference

AFTERNOON MEETINGS

CMA HOUSE OF DELEGATES—Opening Session

San Francisco Dermatological Society Clinical Meeting
Physicians and School Superintendents
Radiology Cancer Conference

SUNDAY, MARCH 24 *MORNING MEETINGS*

L. Henry Garland Memorial Lecture

Section Meetings:

Allergy—and Noon Lunch
Anesthesiology
Dermatology
Internal Medicine—Stanford Medical Center
Orthopedics
Otolaryngology
Radiology

Special Conferences:

California Medical Assistants Association
Pathology Cancer Conference

AFTERNOON MEETINGS

General Meeting: Bleeding and Thrombosis

Section Meetings:

Allergy
Anesthesiology
Ophthalmology
Radiology

MOTION PICTURE PROGRAM: Coronary Artery Disease

Unless stated otherwise, all meeting rooms listed in the programs are in the Fairmont Hotel.

MONDAY, MARCH 25 *MORNING MEETINGS*

General Meeting: Drug Abuse

Section Meetings:

Industrial Medicine
Obstetrics and Gynecology—and Noon Lunch
Physical Medicine—and Noon Lunch
Urology

TELEVISION: (1) Genetics (2) Conjoined Twins

AFTERNOON MEETINGS

General Meeting: Trauma
Alice Stone Woolley Memorial Lecture

Section Meetings:

Internal Medicine—University of California Medical Center
Obstetrics and Gynecology
Urology

MOTION PICTURE PROGRAM: Drug Therapy

TUESDAY, MARCH 26 *MORNING MEETINGS*

General Meeting: Drug Therapy

Section Meetings:

General Surgery
Preventive Medicine and Public Health
Psychiatry and Neurology

Special Conferences:

Disaster Medical Care

TELEVISION: (1) Detection of Uterine Cancer, (2) Sports Injuries

AFTERNOON MEETINGS

HOUSE OF DELEGATES—(4:00 p.m.)

Section Meetings:

Internal Medicine—American College of Cardiology
General Surgery
Psychiatry and Neurology

MOTION PICTURE PROGRAM: Office Diagnosis

Special Conferences:

California Nurses Association: Nurse and Doctor Look at Problems of Manpower

WEDNESDAY, MARCH 27

HOUSE OF DELEGATES—ALL DAY

Section Meetings:

General Practice	ALL DAY
Pediatrics	ALL DAY

Special Conferences:

Environmental Health and Community Design—ALL DAY

TELEVISION: (1) Suicidal Patient, (2) Drug Abuse—MORNING ONLY

special conferences

SATURDAY, MARCH 23 **9:00 a.m.—Venetian Room, Lobby Floor**

SECOND BIENNIAL CONFERENCE

PHYSICIANS AND SCHOOL SUPERINTENDENTS

Committee on School and College Health, California Medical Association

Physicians and Educators Look at Drugs and Sex

A Cooperative Focus at Two Fragments of Health Education

General Chairman: B. Otis Cobb, M.D., Walnut Creek

9:00—**Introduction and Welcome.**

9:15—**Health Education—Problems and Prospects**—Delbert Oberteuffer, Ph.D., Professor Emeritus, Health and Physical Education, Ohio State University, Columbus, Ohio, by invitation.

10:00—**Recess.**

10:15—**Panel on Drugs.**

Moderator: Paul Hillar, Ph.D., Director, Health, Physical Education and Recreation, Stanislaus County Department of Education, Modesto, by invitation.

Members of the Panel: Clifford Jordon, M.D., Coronado Unified School District, Coronado; Haskell L. Bowen, Director, Santa Clara Drug Abuse Information Center, San Jose, by invitation.

11:15—**Discussion.**

Noon—Gold Room, Lobby Floor

12:00—**Townhall Luncheon Meeting**—An opportunity for physicians and educators to talk informally, particularly about health education, drugs and family life education.

SATURDAY, MARCH 23 **2:00 p.m.—Venetian Room, Lobby Floor**

2:00— **Family Life Education and Sex**

Panel Discussion

Moderator: Daniel Collins, D.D.S., Staff, Mount Zion Hospital, San Francisco, by invitation.

Members of the Panel: William Ayres, M.D., San Mateo, Clinical Instructor in Psychiatry, Stanford University School of Medicine; Paul Cook, Anaheim Unified School District, Anaheim, by invitation; Arnim D. Weems, Assistant Superintendent, San Mateo County Government Center, Redwood City, by invitation.

SATURDAY, MARCH 23 **9:15 a.m.—California Room, Mezzanine**

AMERICAN COLLEGE OF CHEST PHYSICIANS CALIFORNIA CHAPTER

Co-Chairmen: David J. Dugan, M.D., and Robert B. Stone, M.D., Oakland

9:15— **Symposium**

Spontaneous Pneumothorax

Speakers to be Announced

10:45—**Recess.**

11:00—**Rehabilitation in C.O.L.D.**—William F. Miller, M.D., Dallas, by invitation.

Noon—Crystal Room Lobby Floor

12:00—**Luncheon and Business Meeting.**

1:00— **Charles E. Smith Memorial Lecture**

Presiding: Maxwell Rosenblatt, M.D., Los Angeles, President, California Chapter, American College of Chest Physicians

1:00—**A Vaccine for Coccidioidomycosis?** (Tentative Title)—Demosthenes Pappagianis, M.D., Davis, by invitation.

SATURDAY, MARCH 23 **2:00 p.m.—California Room, Mezzanine**

2:00— **Symposium**

Acute Respiratory Disease in the Hospital

Speakers to be Announced

2:30—**Medical Management of Acute Asthma**—William F. Miller, M.D., Dallas, by invitation.

3:15—**Panel and Open Discussion.**

4:00—**Recess.**

4:15— **Mystery X-Ray Conference**

Moderator: To be announced.

Members of the Panel: To be announced.

SATURDAY, MARCH 23 9:30 a.m.—French Room Lobby Floor

CONFERENCE ON SMOKING AND HEALTH

Interagency Council on Smoking and Health, California Medical Association

9:30—**The Smoker's Test—An Insight Into Smoking Behavior** — Dan Horn, Ph.D., Arlington, Va., by invitation.

10:30— **Panel Discussion**

Topic to be Announced

Moderator: Cherry Tsutsumida, M.P.H., Arlington, Va., by invitation

Members of the Panel: To be announced.

This program is being presented to introduce the "Smoker's Test" to California physicians. The test is designed for use by physicians in identifying why people smoke and what anti-smoking measure would be most successful with each type of smoker.

SATURDAY, MARCH 23 9:30 a.m. to 5:00 p.m.—Vanderbilt Room, Terrace Floor

RADIOLOGY CONFERENCE

Committee on Cancer, California Medical Association

Chairman: Richard P. Storrs, M.D., Los Angeles

Secretary: Hooshang Taybi, M.D., Oakland

9:30 a.m. to 11:30 a.m.—THERAPY SESSION.

Moderator: Jerome M. Vaeth, M.D., San Francisco

A panel of radiation therapists will discuss radiation therapy of urologic neoplasms. Questions and comments from the floor will be welcomed.

1:30 p.m. to 3:30 p.m.—DIAGNOSTIC SESSION.

Moderator: Richard P. Storrs, M.D., Los Angeles

A series of interesting proven cases of tumor diagnosis will be presented. Audience participation and discussion are urgently requested.

3:30—**California Radiological Society Meeting**—Saul Heiser, M.D., Los Angeles, President, Presiding.

SUNDAY, MARCH 24 9:00 a.m.-5:00 p.m.—Gold Room, Lobby Floor

PATHOLOGY CONFERENCE

Tumors of the Ear, Nose, and Throat

Committee on Cancer, California Medical Association

Chairman: Capt. David D. Rulon, M.C., U.S.N., Oakland, by invitation

Co-Moderators: Malcolm H. McGavarn, M.D., and Walter Bauer, M.D., Department of Pathology, Washington University School of Medicine, St. Louis, Missouri, both by invitation.

9:00 a.m. to Noon—2:00 p.m. to 5:00 p.m.

Those who wish slides and protocols for the Conference (cost, $25.00) are requested to register with Weldon K. Bullock, M.D., Registrar, Tumor Tissue Registry, CMA Committee on Cancer, Los Angeles County Hospital, 1200 North State Street, Los Angeles 90033. The $25 fee includes registration. For those who wish to attend the Conference, the fee is $25. There is no charge for residents and interns.

SPECIAL GENERAL MEETING

SUNDAY, MARCH 24 11:00 a.m.—Hunt Room Mezzanine

Second Annual
L. Henry Garland Memorial Lecture

Sponsored by the California Radiological Society

11:00—**Introduction**—Saul Heiser, M.D., Los Angeles, President, California Radiological Society.

11:05—**The Present Status of Water-Soluble Contrast Media in the Examination of the Acute Abdomen**—Alexander R. Margulis, M.D., San Francisco.

SUNDAY, MARCH 24 9:00 a.m.—Crystal Room Lobby Floor

REVOLUTIONS NEVER GO BACKWARDS

California Medical Assistants Association

General Chairman: Erna L. deNu, C.M.A.A., Castro Valley

Moderator: Charlotte C. Baer, M.D., San Francisco, C.M.A.-C.M.A.A. Liaison Committee

Introductions: Lorene Euler, Culver City, President, C.M.A.A.

Script: Esther Tune, C.M.A.A., Upland

Participants: John G. Morrison, M.D., San Leandro, President, C.M.A.
Eugene D. Clement, M.D., Castro Valley, Consultant, C.M.A.-C.M.A.A. Liaison Committee
Henry Bodner, M.D., Van Nuys, C.M.A.A. Advisory Board of Internal Affairs
Robert D. Huber, LL.B., San Francisco, Legal Counsel, C.M.A.A.
Jeanette Gentile, Walnut Creek, Field Representative, California Blue Shield; Past President, C.M.A.A.
Helen Goldman, San Francisco, Past President, C.M.A.A.
Dorothy Hyde, Fresno, Past President, C.M.A.A.
Eileen Reilly, Castro Valley, C.M.A.A.
Barbara Wade, Los Angeles, Past President, C.M.A.A.

9:00—Vignettes.

10:30—Recess.

11:00— **Panel Discussion**

SPECIAL GENERAL MEETING

MONDAY, MARCH 25 2:00 p.m.—Crystal Room Lobby Floor

Alice Stone Woolley Memorial Lecture

Sponsored by the American Medical Women's Association

2:00—**The Association of Congenital Anomalies of the Urinary Tract with Abnormal Umbilical Cord Vessels and Chromosomal Patterns** — Edith L. Potter, M.D., Fort Myers, Florida, by invitation.

TUESDAY, MARCH 26 9:00 a.m.—Peacock Court Mark Hopkins Hotel

SYMPOSIUM ON DISASTER

Committee on Disaster Medical Care, California Medical Association

General Chairman: Charles C. Henderson, M.D., San Mateo

9:00—**Welcome**—John G. Morrison, M.D., President, California Medical Association, San Leandro.

9:05—**Welcome** — Wayne P. Chesbro, M.D., Chairman, CMA Committee on Disaster Medical Care, Berkeley.

9:10—**Placement of HRDI Units and PDHs in California Hospitals** — Donald E. Barker, M.D., Van Nuys.

9:25—**Formation of the New CMA Committee on Emergency Medical Care** — Carl E. Anderson, M.D., Santa Rosa.

9:40—**Transfer of the Medical and Health Division, California Disaster Office, to the California State Department of Public Health**—Julian A. Waller, M.D., Berkeley.

9:55—**Medical Aspects of Civil Strife in Berkeley and Oakland, 1967**—Wayne P. Chesbro, M.D., Berkeley.

10:10—**Hospital Preparedness for Riot Emergencies** —Leslie R. Smith, Chairman, California Hospital Association Task Force on Emergency Health Services, Torrance, by invitation.

10:30—**Questions and Answers.**

10:45—**California Emergency Resources Management Plan** — Florence R. Weiner, R.N., Bureau of Emergency Health Services, California Department of Public Health, Berkeley, by invitation.

11:00—**Emergency Operating Center—Demonstration of Test Exercise.**
Test Director: Charles G. Henderson, M.D., San Mateo

Emergency and Health Operation Staff:
Chief
Julian A. Waller, M.D., Berkeley
Deputy Chief
Wayne P. Chesbro, M.D., Berkeley
Chief, Medical Division
Frank F. Schade, M.D., Los Angeles
Chief, Health Manpower Division
John T. McNally, M.D., Stockton
Chief, Supply Division
William McLarty, Berkeley, by invitation.
Dental Consultant
Myron E. Horan, D.D.S., San Francisco, by invitation.
Nursing Consultant
Florence R. Weiner, R.N., Berkeley, by invitation.
Pharmaceutical Consultant
George E. Nicholau, Marysville, by invitation.
Hospital Administration Consultant
Leslie R. Smith, Torrance, by invitation.
Sanitary Engineer
Glen E. Browning, Sacramento, by invitation.
Administrative and Federal Liaison Officer
Edward P. Patton, Sacramento, by invitation.

TUESDAY, MARCH 26 2:00 p.m.—Crystal Room Lobby Floor

THE NURSE AND DOCTOR LOOK AT PROBLEMS OF MANPOWER

Presented by the California Nurses Association and the California Medical Association

Chairman: C. Gerald Scarborough, M.D., San Jose

2:00—**What are the Problems?**—Donald P. MacDonald, M.D., San Francisco, by invitation.

2:20—**How the California Manpower Council Will Help** — Kenneth L. Briney, Ph.D., San Francisco, and Edna J. Brandt, M.S., M.A., Berkeley, both by invitation; and C. Gerald Scarborough, M.D., San Jose.

3:00—**Panel Discussion** — Immunizations, Coronary Care Units, Midwifery, Physicians' Aides, Patient Education and Others. (Problems and questions to be submitted from the Audience.)

Moderator: Roger O. Egeberg, M.D., Los Angeles

Members of the Panel: Grace C. Barbee, J.D., San Francisco; Robert D. Huber, LL.B., San Francisco; and Lillian E. Brown, B.S., Orange, all by invitation; Herbert Bauer, M.D., Woodland; C. Gerald Scarborough, M.D., and Malcolm R. Parker, M.D., both San Jose.

WEDNESDAY, MARCH 27 9:00 a.m.-4:00 p.m.—California Room, Mezzanine

ENVIRONMENTAL HEALTH CONFERENCE

Committee on Environmental Health, California Medical Association

Symposium

Environmental Health and Community Design

Chairman: John R. Goldsmith, M.D., Berkeley

Program to be Announced.

● GENERAL MEETINGS

FIRST GENERAL MEETING

SUNDAY, MARCH 24 **2:00 p.m.—Venetian Room Lobby Floor**

Symposium

The Bleeding Syndromes and Thrombosis

Moderator: Garson H. Tishkoff, M.D., Los Angeles

2:00—**Introductory Remarks** — Garson H. Tishkoff, M.D., Los Angeles.

2:05—**The Bleeder — Hemophilia or the Devil's Pinch** — Cecil Hougie, M.D., Seattle, Washington, by invitation.

2:35—**Local Thrombosis — Or Something More?** — Daniel Deykin, M.D., Boston, Massachusetts, by invitation.

3:05—**Recess.**

3:15—**Blood, Plasma, and Protein Concentrates**—Paul M. Aggeler, M.D., San Francisco.

3:45—**Oral Contraceptives—What are the Risks of Thrombosis?**—Arthur J. Samuels, M.D., Beverly Hills.

4:15— **Panel Discussion**

Diagnostic Tests—What Do They Mean?

Moderator: Garson H. Tishkoff, M.D., Los Angeles

Members of the Panel: Cecil Hougie, M.D., Seattle, Daniel Deykin, M.D., Boston, both by invitation; Paul M. Aggeler, M.D., San Francisco, and Arthur J. Samuels, M.D., Beverly Hills.

VISIT TECHNICAL AND SCIENTIFIC EXHIBITS

SECOND GENERAL MEETING

MONDAY, MARCH 25 **9:00 a.m.—Venetian Room Lobby Floor**

Panel Discussion

Current Problems of Drug Abuse—
"Pot, Acid and Speed"

Moderator: J. Thomas Ungerleider, M.D., Los Angeles

9:00—**Introduction of Panelists** — J. Thomas Ungerleider, M.D., Los Angeles.

9:20—**Drug Abuse Today — The M.A.D. (Mind Altering Drug) World** — Joel Fort, M.D., San Francisco, by invitation.

9:40—**The Marijuana Problem—Past, Present, and Future** —Tod H. Mikuriya, M.D., Morrisville, Pa., by invitation.

10:00—**L.S.D. Revisited — Adolescence and Psychedelia** — Duke D. Fisher, M.D., Los Angeles, by invitation.

10:20—**Patterns of Amphetamine Abuse**—David E. Smith, M.D., San Francisco, by invitation.

10:40—**Conclusion**—James L. Goddard, M.D., Washington, D.C., by invitation.

11:00—**Intra-Panel Discussion and Audience Question and Answer Period** — Microphones will be set up throughout the auditorium.

THIRD GENERAL MEETING

MONDAY, MARCH 25 **1:30 p.m.—Venetian Room Lobby Floor**

Symposium on Trauma

Moderator: Carleton Mathewson, Jr., M.D., San Francisco

1:30—**Introduction** — Carleton Mathewson, Jr., M.D., San Francisco.

1:40—**Evaluation and Emergency Management of the Acutely Injured, With Particular Reference to Traumatic Shock**—F. William Blaisdell, M.D., San Francisco.

2:00—**Head Injuries** — Byron C. Pevehouse, M.D., San Francisco.

2:20—**Penetrating Wounds of the Neck**—Thomas K. Hunt, M.D., San Francisco.

2:40—**Management of Civilian Thoracic Trauma**—David J. Dugan, M.D., Oakland.

3:00—**Recess.**

3:40—**Penetrating Wounds of the Abdomen** — Bert L. Halter, M.D., San Francisco.

4:00—**Blunt Wounds of the Abdomen**—Grosvenor T. Root, M.D., Oakland.

4:20—**Recognition and Management of Injuries to the Genito-Urinary Tract**—Jerome M. Weiss, M.D., San Francisco, by invitation.

4:40—**Vascular Injuries** — Colonel Arthur Cohen, M.C., U.S.A., San Francisco, by invitation.

(Continued on next page)

ATTENTION:

CHECK TELEVISION AND MOTION PICTURE PROGRAMS, PAGES 34-36

FOURTH GENERAL MEETING

TUESDAY, MARCH 26 **9:00 a.m.—Venetian Room Lobby Floor**

To Be Or Not To Be — Effective Drug Therapy: The Government and the Academicians Answer

Moderator: Kenneth L. Melmon, M.D., San Francisco, by invitation.

9:00—**The Federal Drug Administration's Role in the Future of Drug Investigation and Therapeutics** — James L. Goddard, M.D., Washington, D.C., by invitation.

9:30—**Clinical Pharmacology and Changing Concepts of Drug Reactions**—Kenneth L. Melmon, M.D., San Francisco, by invitation.

10:00—**A Guide to Meaningful Interpretation of Therapeutic Claims** — John A. Oates, M.D., Nashville, Tennessee, by invitation.

10:30—**Therapeutics of Heart Failure—An Example of the Complexity of Drug Selection**—Charles A. Chidsey, III, M.D., Denver, Colorado, by invitation.

11:00—**Detection and Practical Meaning of Drug Interactions**—Howard F. Morrelli, M.D., San Francisco, by invitation.

11:30— **Panel Discussion**

Problems of Communication Between the Government, Science, and a Doctor

Moderator: Kenneth L. Melmon, M.D., San Francisco, by invitation

Members of the Panel: James L. Goddard, M.D., Washington, D. C., John A. Oates, M.D., Nashville, Tennessee, Charles A. Chidsey, III, M.D., Denver, Colorado, Howard F. Morrelli, M.D., San Francisco, all by invitation.

VISIT TECHNICAL EXHIBITS

GENERAL SURGERY

Chairman.....ALBERT G. CLARK, M.D., SAN FRANCISCO
Secretary.....ROBERT T. HOOD, JR., M.D., VAN NUYS
Assistant Secretary. HAROLD H. LINDNER, M.D., SAN FRANCISCO

TUESDAY, MARCH 26 **9:00 a.m.—French Room Lobby Floor**

9:00—**Anatomy of the Inguinal Region**—Harold H. Lindner, M.D., San Francisco.

9:20—**The Bassini Procedure**—F. William Blaisdell, M.D., San Francisco.

9:40—**The McVay Procedure** — Chester B. McVay, M.D., Yankton, South Dakota, by invitation.

10:00—**Inguinal Hernia in Infancy and Childhood** — Harry E. Peters, M.D., Oakland.

10:20—**Preperitoneal Repair of Hernias** — Colonel Arthur Cohen, M.C., U.S.A., San Francisco, by invitation.

10:40—**Recess.**

11:00— **General Discussion Period**

Moderator: Chester B. McVay, M.D., Yankton, South Dakota, by invitation.

Microphones will be set up throughout the auditorium so that the audience may ask questions.

TUESDAY, MARCH 26 **1:30 p.m.—French Room Lobby Floor**

1:30—**Treatment of Burns at San Francisco General Hospital**—David G. Fraser, M.D., San Francisco, by invitation.

1:50—**Fluid and Electrolyte Replacement in Burns** — Thomas K. Hunt, M.D., San Francisco.

2:10—**A Plastic Surgeon Looks at Burns** — Vincent R. Pennisi, M.D., D.D.S., San Francisco.

2:30—**Recess.**

2:45—**Cloacogenic Anorectal Junctional Cancer** — Lewis I. Grodsky, M.D., San Francisco.

3:10—**Short Bowel Syndrome** — Yorke G. Jacobson, M.D., Pittsburg.

3:30—**Surgical Procedures in the Treatment of Chronic Ulcerative Colitis** — B. Richard Jackson, M.D., Los Angeles.

3:50—**Chairman's Address** — Albert G. Clark, M.D., San Francisco.

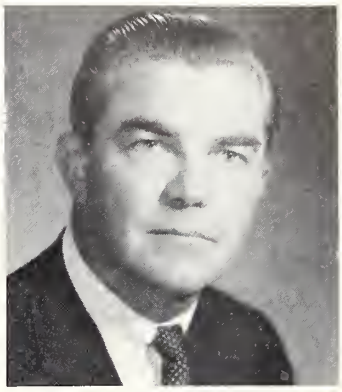
4:10—**Business Meeting.**

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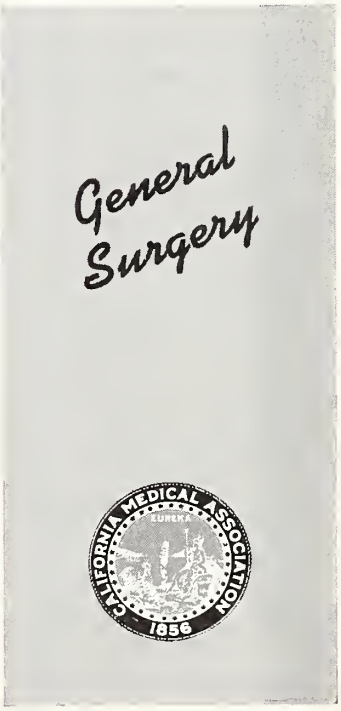
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ALBERT G. CLARK
Chairman



ROBERT T. HOOD, JR.
Secretary

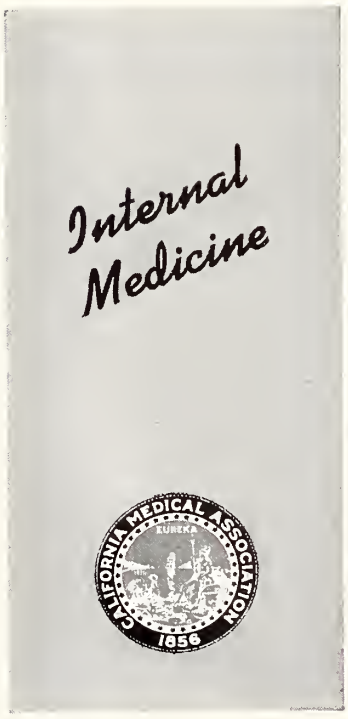




JOHN L. BENTON
Chairman



LEYLAND E. STEVENS
Secretary



INTERNAL MEDICINE

Chairman JOHN L. BENTON, M.D., LOS ANGELES
Secretary LEYLAND E. STEVENS, M.D., SAN FRANCISCO
Assistant Secretary PETTUS G. SECREST, M.D., LONG BEACH

SUNDAY, MARCH 24 **9:30 a.m.—Venetian Room Lobby Floor**

Presented by Stanford University School of Medicine

9:30— Immunology

Chairman: Halsted R. Holman, M.D., Professor of Medicine, Stanford University, Palo Alto, by invitation.

Following each presentation there will be a ten-minute Discussion Period. Microphones will be set up throughout the auditorium so that the audience may ask questions.

9:30—**Diseases with Abnormal Gamma Globulins** — Hugh O. McDevitt, M.D., Palo Alto, by invitation.

10:00—**Current Status of Auto-immunity**—Gordon C. Sharp, M.D., Palo Alto, by invitation.

10:30—**Recent Advances on Glomerulonephritis** — Kenneth L. Vosti, M.D., Palo Alto, by invitation.

11:00—**Resistance to Virus Infection**—Thomas C. Merigan, Jr., M.D., Palo Alto, by invitation.

11:30—**Immunology of Tissue Transplantation**—Halsted R. Holman, M.D., Palo Alto, by invitation.

MONDAY, MARCH 25 **2:00 p.m.—French Room Lobby Floor**

Presented by the Department of Medicine, University of California Medical Center, San Francisco

2:00— Endocrinology

Chairman: Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine, University of California Medical Center, San Francisco, by invitation.

Following each presentation there will be a five-minute Discussion Period. Microphones will be set up throughout the auditorium so that the audience may ask questions.

2:00—**Acromegaly—Diagnosis and Treatment**—Lowell L. Sparks, M.D., San Francisco, by invitation.

2:30—**Differential Diagnosis of Hirsutism** — Lawrence C. Wagienka, M.D., San Francisco, by invitation.

3:00—**Early Recognition and Treatment of Diabetes** — Peter H. Forsham, M.D., San Francisco.

3:30—**Recent Developments in Diagnosis and Management of Hyperthyroidism** — Francis S. Greenspan, M.D., San Francisco.

4:00—**Endocrine Hypertension**—Edward G. Biglieri, M.D., San Francisco.

4:30—**Business Meeting.**

TUESDAY, MARCH 26 **2:00 p.m.—Venetian Room Lobby Floor**

Presented Jointly by the Section on Internal Medicine and The American College of Cardiology

Co-moderators: John J. Sampson, M.D., San Francisco
J. Douglas McNair, M.D., Arcadia

2:00—**Action of Diuretics in Heart Failure**—Laurence E. Earley, M.D., San Francisco, by invitation.

2:40—**Clinical Use of Beta Blockage**—Donald C. Harrison, M.D., Palo Alto, by invitation.

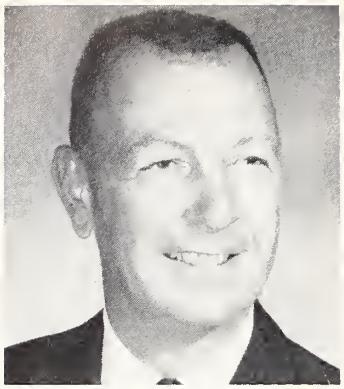
3:15—**Recess.**

3:30—**Relation of Catechols to Heart Failure**—Charles A. Chidsey, III, M.D., Denver, by invitation.

4:10—**The Mechanics and the Management of Non-Surgical Shock** — Kenneth L. Melmon, M.D., San Francisco, by invitation.

4:45—**Colloquia with Afternoon Lecturers.**

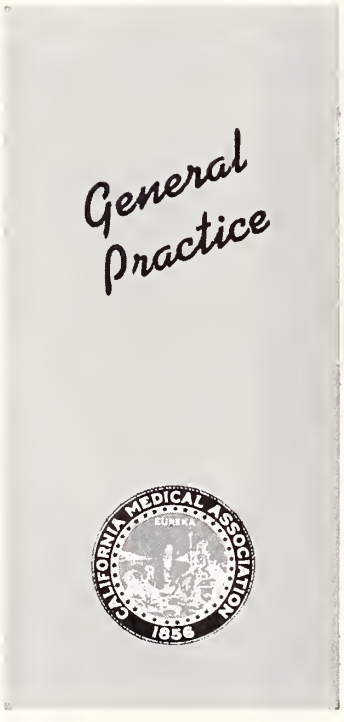
VISIT TECHNICAL AND SCIENTIFIC EXHIBITS



ALFRED F. KANDLBINDER
Chairman



ALLEN F. STERLING
Secretary



GENERAL PRACTICE

Chairman ALFRED F. KANDLBINDER, M.D., MONTEREY
Secretary ALLEN F. STERLING, M.D., SAN BERNARDINO
Assistant Secretary ROBERT F. GOBAR, M.D., DALY CITY

WEDNESDAY, MARCH 27 9:00 a.m.—Venetian Room Lobby Floor

Combined Meeting with Section on Pediatrics

9:00—**Introduction**—Sherrod C. Swift, M.D., Whittier.

9:05—**Basic Concepts of Viral Disease—Past and Present**—A. Frederick Rasmussen, M.D., Los Angeles, by invitation.

10:00—**The Immune Response of the Human With Particular Reference to Multiple Immunizations**—Paul F. Wehrle, M.D., Los Angeles.

10:50—**Recess.**

11:10—**Influenza and Other Viral Respiratory Infections**—Dorthy M. Horstmann, M.D., New Haven, Connecticut, by invitation.

12:15—**Business Meeting—General Practice.**

WEDNESDAY, MARCH 27 1:00 p.m.—Venetian Room Lobby Floor

Combined Meeting with Section on Pediatrics

1:00—**Recent Advances in Rubella**—Paul D. Parkman, M.D., Bethesda, Maryland, by invitation.

1:50—**Recent Concepts in Prevention and Immunization Against Viral Disease**—Samuel Baron, M.D., Bethesda, Maryland, by invitation.

2:40—**Recess.**

3:00—**The Laboratory Diagnosis of Viral Disease**—Speaker to be announced.

3:30—**Panel Discussion: Question and Answer Session.**

Moderator: Sherrod C. Swift, M.D., Whittier

Members of the Panel: A. Frederick Rasmussen, M.D., Los Angeles, by invitation; Paul F. Wehrle, M.D., Los Angeles; Dorothy M. Horstmann, M.D., New Haven, Connecticut, by invitation; Paul D. Parkman, M.D., Bethesda, Maryland, by invitation; Samuel Baron, M.D., Bethesda, Maryland, by invitation.

4:00—**Business Meeting—Pediatrics.**

ALLERGY

Chairman ERNEST J. SASLOW, M.D., BAKERSFIELD
Secretary SAMUEL ROSS, M.D., FRESNO
Assistant Secretary BAILEY J. LOVIN, M.D., RESEDA

SUNDAY, MARCH 24 **9:00 a.m.—Vanderbilt Room Terrace Floor**

9:00—**Asthma Due to Candida Albicans**—Robert W. Robinett, M.D., Los Angeles.

9:30—**Pollens, Plants, and Allergy in Southern California**—Daniel Gorenberg, M.D., San Bernardino.

10:00—**Treatment for Prophylaxis Against Poison Oak Dermatitis**—William L. Epstein, M.D., San Francisco.

10:30—**Immunoglobulins—Practical Considerations in Allergy**—Herbert S. Kaufman, M.D., San Francisco.

11:15—**The Psychiatrist Looks at the Asthmatic Child**—Thomas J. McDermott, M.D., Glendale.

SUNDAY, MARCH 24 **Noon—Pavilion Room Lobby Floor**

12:00—Luncheon and Business Meeting with the California Society of Allergy.

SUNDAY, MARCH 24 **2:00 p.m.—Vanderbilt Room Terrace Floor**

2:00—**The Use of Corticosteroids in Allergy**—Vincent C. DiRaimondo, M.D., San Francisco, by invitation.

2:45—**Regional Enteritis—Allergy in Its Etiology**—Albert H. Rowe, M.D., Oakland.

3:15—**The Anesthesiologist and the Asthmatic Patient**—Joseph Lee, M.D., San Francisco, by invitation.

3:45—**Status Asthmaticus in Children: Pathophysiology and Management**—Warren Richards, M.D., Los Angeles.

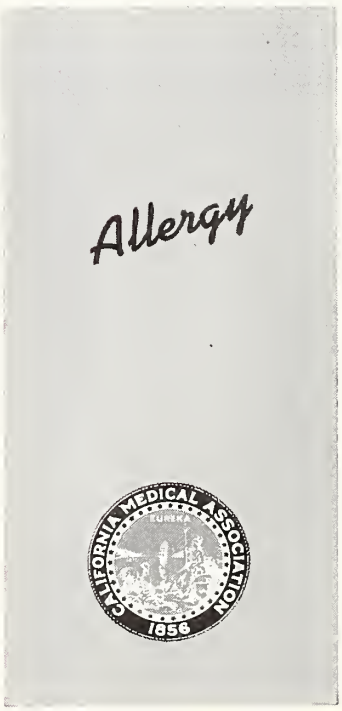
4:30—**Incidence of Positive Skin Tests Among Medical Students**—Ned J. Whitcomb, M.D., San Francisco, by invitation.



ERNEST J. SASLOW
Chairman



SAMUEL ROSS
Secretary

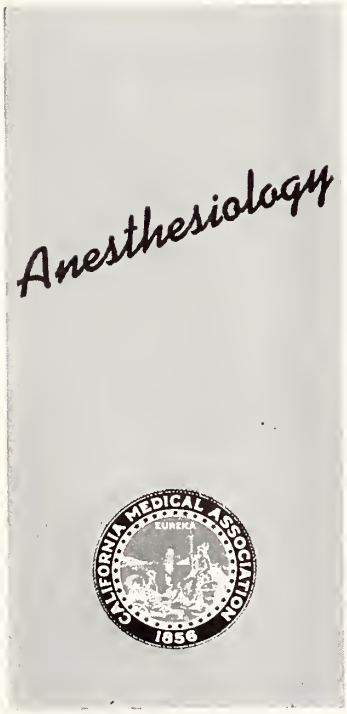




DONALD B. DOSE
Chairman



DONALD A. WALKER
Secretary



ANESTHESIOLOGY

Chairman DONALD B. DOSE, M.D., SAN DIEGO
Secretary DONALD A. WALKER, M.D., TIBURON
Assistant Secretary HAMILTON S. DAVIS, M.D., DAVIS

SUNDAY, MARCH 24 **9:00 a.m.—Garden Room Lobby Floor Other Rooms to be Announced**

Program Coordinator: Donald A. Walker, M.D., Tiburon

9:00—**Coordination of Meeting**—Announcement of Topics and Room Assignments.

Several small round tables are planned, each with two co-chairmen and seats for a participating audience of eight. Topics for discussion will generally follow the interests of the co-chairmen, but considerable leeway is anticipated. Discussion periods will be one hour each, with two periods in the morning and two in the afternoon.

9:30—**Round Table Discussions**—To be held in rooms assigned at 9:00 a.m.

Round Table Co-Chairmen:

Verne L. Brechner, M.D., Los Angeles.
Henry A. Condon, F.F.A.R.C.S., London, England, by invitation.
Hamilton S. Davis, M.D., Davis.
Thomas J. DeKornfeld, M.D., Ann Arbor, Michigan, by invitation.
Grant Fletcher, M.D., Palo Alto.
Ernest P. Guy, M.D., Tiburon.
William K. Hamilton, M.D., San Francisco, by invitation.
C. Philip Larson, Jr., M.D., San Francisco.
William F. Miller, M.D., Dallas, Texas, by invitation.
Robert T. Patrick, M.D., Davis, by invitation.
Sol M. Shnider, M.D., San Francisco.
Morley M. Singer, M.D., San Francisco.
C. Ronald Stephen, M.D., Dallas, Texas, by invitation.
Carl E. Wasmuth, M.D., Cleveland, Ohio, by invitation.

SUNDAY, MARCH 24 **1:30 p.m.—Rooms as Assigned in Morning Session**

1:30—**Continuation of Round Table Discussions.**

2:30—**Recess.**

3:00—**Continuation of Round Table Discussions.**

4:00 p.m.—Far East Room Mezzanine

4:00—**Business Meeting.**

Those who plan to attend the Round Table Discussions are requested to notify Doctor Eugene G. Miller, 693 Sutter Street, San Francisco 94102, so that adequate facilities can be provided.

DERMATOLOGY

Chairman SAMUEL AYRES, III, M.D., BEVERLY HILLS
Secretary GEORGE T. WILSON, M.D., PALO ALTO
Assistant Secretary CHARLES G. STEFFEN, M.D., COVINA



SAMUEL AYRES, III
Chairman



GEORGE T. WILSON
Secretary

SATURDAY, MARCH 23
2:00 p.m.—Room 344, Clinics Building
University of California Medical Center
3rd and Parnassus Avenues
San Francisco

Preconvention Meeting

There will be a clinical meeting of the San Francisco Dermatological Society at 2:00 p.m. Discussion of the cases will take place at 3:00 p.m., in the Main Auditorium of the Medical Sciences Building. This will be followed by a no-host cocktail party and dinner, the site of which will be announced. A speaker with a subject of interest to dermatologists and their wives will entertain you. All dermatologists are invited by the San Francisco Dermatological Society to attend.

SUNDAY, MARCH 24
9:00 a.m.—Exhibit Hall, Masonic Temple
California St. near Taylor

9:00—**The Reconstruction of the Skin by Transplanted Epithelial Cell Cultures**—Marvin A. Karasek, Ph.D., Palo Alto, by invitation.

9:20—**Electron Microscopy as an Aid to the Dermatologist**—Alvin J. Cox, Jr., M.D., Palo Alto.

9:40—**Immunologic Studies in Atopic Dermatitis** — Harry L. Roth, M.D., Daly City.

10:00—**Phototesting Techniques for Photocontact and Drug Photosensitivity Problems**—John H. Epstein, M.D., San Francisco.

10:20—**Recess.**

10:30—**Carcinomas Associated with Burns and Scars**—Leo Indianer, M.D., Encino.

10:50—**The Role of Cutaneous Microflora in the Pathogenesis of Acne—Biochemical and Immunologic Considerations**—Ronald M. Reisner, M.D., Torrance.

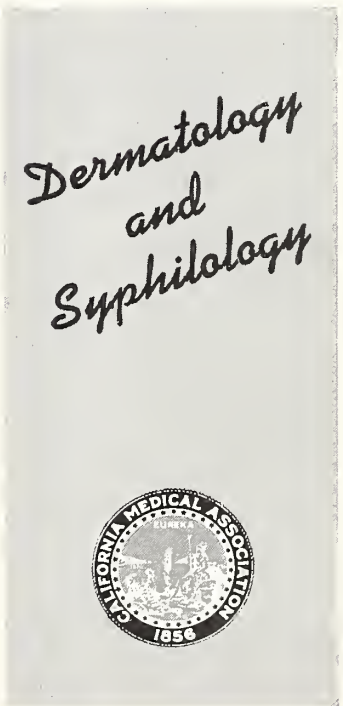
11:10—**Pityriasis Rubra Pilaris** — Daniel A. Gross, M.D., Reseda.

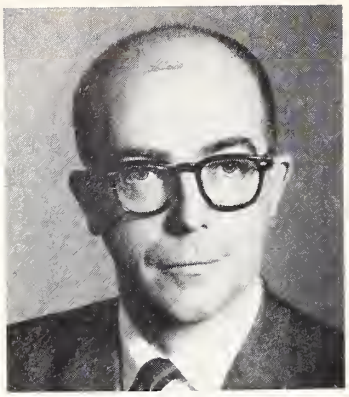
11:25—**Chairman's Address**—Samuel Ayres III, M.D., Beverly Hills.

11:35—**Newer Concepts of Granulomas in Dermatology**—William L. Epstein, M.D., San Francisco.

11:50—**Topical Nitrogen Mustard in Mysocis Fungoids**—Faye D. Arundell, M.D., Palo Alto, by invitation.

12:05—**Business Meeting.**

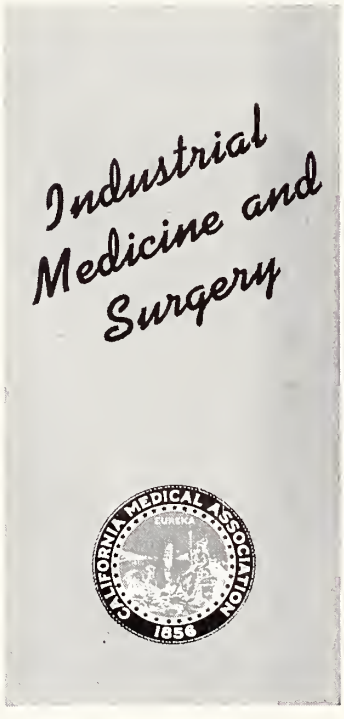




RAYMOND O. OJA
Chairman



JAMES G. FORGERSON
Secretary



INDUSTRIAL MEDICINE AND SURGERY

Chairman..... RAYMOND O. OJA, M.D., SAN FRANCISCO
Secretary..... JAMES G. FORGERSON, M.D., SAN FRANCISCO
Assistant Secretary.... DAVID P. DISCHER, M.D., LOS ANGELES

MONDAY, MARCH 25 **9:00 a.m.—Vanderbilt Room Terrace Floor**

Combined Meeting with Section on Physical Medicine

9:00—**Thoughts on Rehabilitation** — Lorin L. Stephens, M.D., Arcadia.

9:45—Recess.

10:00— **Panel Discussion**

Is Physical Therapy Rehabilitation?

Moderator: Bernard J. Michela, M.D., Long Beach

Members of the Panel: Robert C. Geiger, M.D., Sonoma; Raymond O. Oja, M.D., San Francisco; William de la Joie, M.D., Los Angeles, by invitation; Donald E. Lamond, M.D., Stockton; and Royce P. Noland, R.P.T., Santa Cruz, by invitation.

12:30—**Business Meeting—Industrial Medicine.**

MESSAGE CENTER

MESSAGE CENTER (415 781-4300)—*Provided through the courtesy of the Pacific Telephone and Telegraph Company* — Registration Desk, Main Lobby, Fairmont Hotel—Registration Desk is open from 8:00 a.m. until 5:00 p.m. — The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the convention number. Routine messages will be kept at the Message Center in the Fairmont Hotel Lobby.

Physicians are requested to check with the Message Center at least once a day.

OBSTETRICS AND GYNECOLOGY

Chairman WARREN E. JONES, M.D., SACRAMENTO
Secretary JAMES W. RAVENSCROFT, M.D., SAN DIEGO
Assistant Secretary CLIFFORD C. CHAPPELL, M.D., BERKELEY

MONDAY, MARCH 25 **9:30 a.m.—French Room**
Lobby Floor
Fairmont Hotel

9:30—**Culdocentesis and the Early Diagnosis of Ovarian Carcinoma** — Gerald S. Bernstein, M.D., Los Angeles, by invitation.

10:00—**Cryosurgery on the Uterine Cervix** — Duane E. Townsend, M.D., Los Angeles, by invitation.

10:30—**Air Embolism as a Cause of Obstetrical Death** — Lester T. Hibbard, M.D., Los Angeles.

11:00—**Chairman's Address** — Warren E. Jones, M.D., Sacramento.

MONDAY, MARCH 25 12:00 noon—Golden Empire Suite
Mark Hopkins Hotel

12:00—**Joint Luncheon Meeting with the California Division of the American College of Obstetricians and Gynecologists.** Advance reservations are necessary, and may be made with Clifford C. Chappell, M.D., 3031 Telegraph Avenue, Berkeley 94705, (415) 845-4200. Price: Approximately $5.00.

1:00—**Current Status of the Prevention of RH Sensitization**—H. Herbert Dibbern, M.D., Long Beach, by invitation.

MONDAY, MARCH 25 **2:00 p.m.—Crystal Room**
Lobby Floor
Fairmont Hotel

Combined Meeting with Section on Urology

Alice Stone Woolley Memorial Lecture

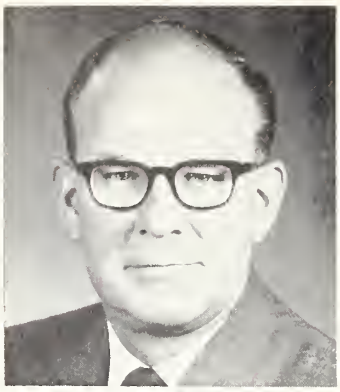
Sponsored by the American Medical Women's Association

2:00—**The Association of Congenital Anomalies of the Urinary Tract with Abnormal Umbilical Cord Vessels and Chromosomal Patterns** — Edith L. Potter, M.D., Fort Myers, Florida, by invitation.

3:00—**Renal Hemodynamics and Sodium Excretion** — Charles A. Chidsey, III, M.D., Denver, Colorado, by invitation.

3:30—**Recess** (Urology Section to return to Florentine Room for their Business Meeting.)

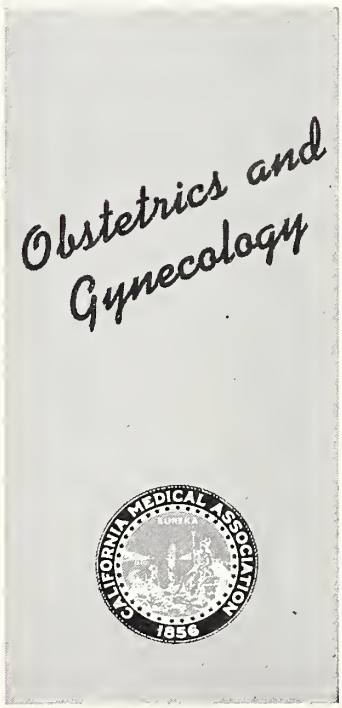
3:35—**Business Meeting.**



WARREN E. JONES
Chairman



JAMES W. RAVENSCROFT
Secretary

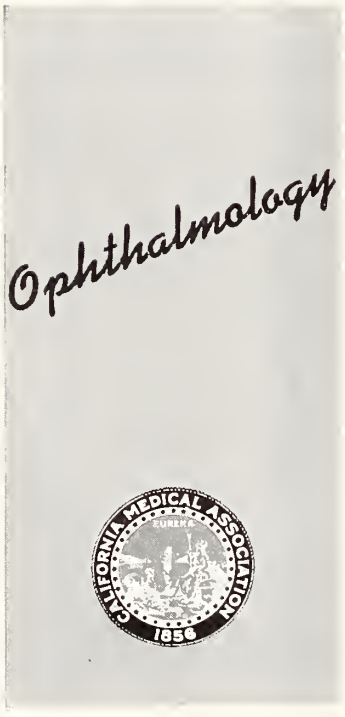




WENDELL C. IRVINE
Chairman



ROBERT E. HOPKINS
Secretary



OPHTHALMOLOGY

Chairman WENDELL C. IRVINE, M.D., LOS ANGELES
Secretary ROBERT E. HOPKINS, M.D., STOCKTON
Assistant Secretary JUNE P. MCBRIDE, M.D., LOS ANGELES

SUNDAY, MARCH 24 **2:00 p.m.—French Room Lobby Floor**

2:00—**Measurements in Strabismus** — Robert L. Tour, M.D., San Francisco.

2:30—**Dyslexia**—Earl L. Stern, M.D., San Francisco.

3:00—**Photocoagulation as an Adjunct to Cryohypophysectomy**—Nathan H. Roth, M.D., Pasadena.

3:30—**Keratoplasty for Inflammatory Corneal Disease** — Thomas E. Moore, Jr., M.D., San Francisco.

4:00—**Business Meeting and Election of Officers.**

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VISIT TECHNICAL AND SCIENTIFIC EXHIBITS

ORTHOPEDICS

Chairman ARTHUR R. HARTWIG, M.D., SAN FRANCISCO
Secretary VERNON L. SMYTHE, M.D., LOS ANGELES
Assistant Secretary JOHN A. BLOSSER, M.D., OAKLAND

SUNDAY, MARCH 24 **9:15 a.m.—French Room Lobby Floor**

9:15— **Round Table Conference**

"Simple" Orthopedic Cases with Problem Complications

Moderator: Arthur R. Hartwig, M.D., San Francisco

Following each presentation there will be a general Discussion Period. Microphones will be set up throughout the auditorium. Audience participation is keenly anticipated.

1. **Wrist Fractures—Why Did It Displace?**—Edwin G. Bovill, M.D., San Francisco.
2. **Disabling Shoulder Pain — Neuritis? Bursitis? Cuff Tear?**—Carl E. Horn, M.D., Sacramento.
3. **Ankle Injuries—Is a Sprain Worse Than a "Clean Break"?** — Floyd H. Jergesen, M.D., San Francisco.
4. **Pathologic Bony Shadows — Benign or Malignant?**—J. Vernon Luck, M.D., Los Angeles.
5. **Fractures in Children—Will Growth Correct the Deformity?**—John C. Wilson, Jr., M.D., Los Angeles.

12:15—**Business Meeting.**

REGISTRATION

Registration and information desks are located in the Main Lobby of the Fairmont Hotel. *All members, guests, and visitors are requested to register immediately upon arrival.* There is no charge for registration. Registration desks are open Saturday through Wednesday. *Admission to the general and section sessions, and exhibit area is by badge only.*

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

ATTENTION:

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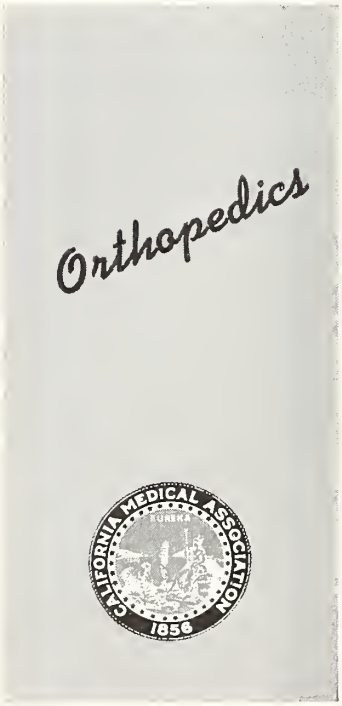
BRING PROPER IDENTIFICATION FOR REGISTRATION



ARTHUR R. HARTWIG
Chairman



VERNON L. SMYTHE
Secretary

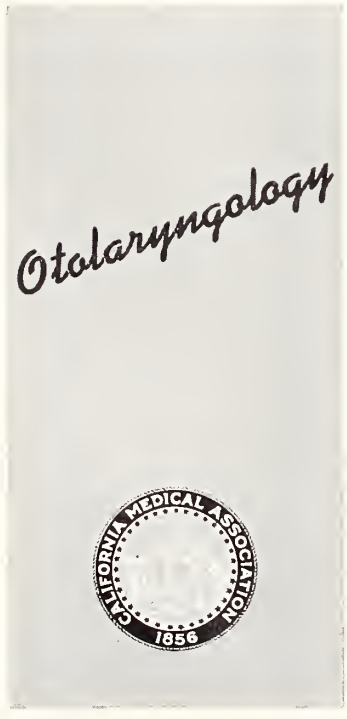




CHARLES P. LEBO
Chairman



IRVING L. WHITE
Secretary



OTOLARYNGOLOGY

Chairman.....CHARLES P. LEBO, M.D., SAN FRANCISCO
Secretary.....IRVING L. WHITE, M.D., LONG BEACH
Assistant Secretary.....EMILE GOUGH, M.D., STOCKTON

SUNDAY, MARCH 24 **9:30 a.m.—Florentine Room Mezzanine**

9:30—**Non-Otologic Aspects of Deafness**—Hilde S. Schlesinger, M.D., San Francisco, by invitation.

9:50—**Cortical Audiometry**—F. Mark Rafaty, M.D., Palo Alto, by invitation.

10:10—**Sudden Deafness**—F. Blair Simmons, M.D., Palo Alto.

10:30—**Follow-up Studies in Patients with Middle Ear Drain**—R. Melvin Butler, M.D., Pomona.

10:50—**Cryotherapy in Palliation of Head and Neck Tumors**—Richard L. Goode, M.D., Palo Alto.

11:10—**Injection Treatment of Paralyzed Vocal Cords**—Henry J. Rubin, M.D., Beverly Hills.

11:30—**Business Meeting.**

VISIT TECHNICAL AND SCIENTIFIC EXHIBITS

BRING PROPER IDENTIFICATION FOR REGISTRATION

PATHOLOGY

Chairman..... WILLIAM H. KERN, M.D., LOS ANGELES
Secretary..... DONALD L. BITTNER, M.D., SAN FRANCISCO
Assistant Secretary..... JEROME L. HEARD, M.D., SAN DIEGO

SATURDAY, MARCH 23 **9:00 a.m.—Hunt Room Mezzanine**

9:00—**Chemistry Screening Panels—One Year of Experience:**

1. Reagents, Methodology and Equipment—Problems and Solutions—Richard F. Straw, Ph.D., by invitation; and Charles M. Blumenfeld, M.D., Sacramento.
2. Normal and Abnormal Data—Clinical Applications — Charles M. Blumenfeld, M.D., Sacramento.

9:30—**Continuous Versus Discrete Automated Analysis**—Bernard J. Poletti, M.D., Los Angeles.

9:45—**A Rapid Method for Integrating Densitometry Curves**—R. Eugene Tolls, M.D., San Francisco.

10:00—**Clinical Experience With a Rapid Plasma Cortisol Determination—Specificity and Normal Values**—Richard J. Grechman, M.D., by invitation; and Donald L. Bittner, M.D., San Francisco.

10:15—**Laboratory Diagnosis of Intravascular Clotting Syndromes**—Cecil Hougie, M.D., Seattle, by invitation.

10:35—**Recess.**

10:40—**Hypomagnesemia in Acute Leukemia**—Paul T. Wertlake, M.D., Los Angeles.

10:55—**Chairman's Address: Pathology of Lung Cancer in Long-Term Survivors**—William H. Kern, M.D., Los Angeles.

11:10—**Extranodal Malignant Lymphomas and Pseudolymphomas**—Sidney L. Saltzstein, M.D., San Diego.

11:30—**Lysogeny and Viral Neoplasis**—David Korn, M.D., Palo Alto, by invitation.

11:50—**Business Meeting.**

SUNDAY, MARCH 24 **9:00 a.m.-5:00 p.m.—Gold Room Lobby Floor**

PATHOLOGY CONFERENCE

Tumors of the Ear, Nose, and Throat

Committee on Cancer, California Medical Association

Chairman: Capt. David D. Rulon, M.C., U.S.N., Oakland, by invitation.

Co-Moderators: Malcolm H. McGavarn, M.D., and Walter Bauer, M.D., St. Louis, Missouri, both by invitation.

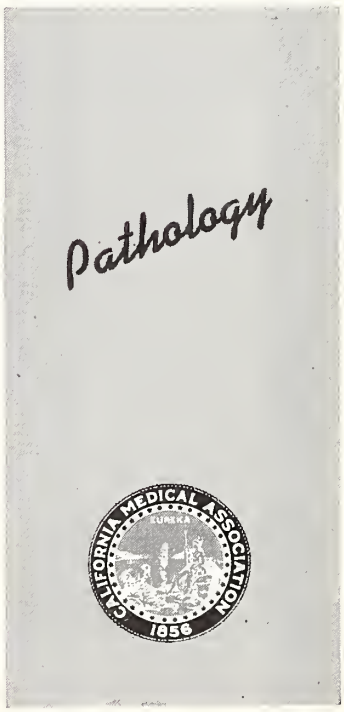
9:00 a.m. to Noon—2:00 p.m. to 5:00 p.m.
Those who wish slides and protocols for the Conference (cost, $25.00) are requested to register with Weldon K. Bullock, M.D., Registrar, Tumor Tissue Registry, CMA Committee on Cancer, Los Angeles County Hospital, 1200 North State Street, Los Angeles 90033. The $25 fee includes registration. For those who wish to attend the Conference, the fee is $25. There is no charge for residents and interns.

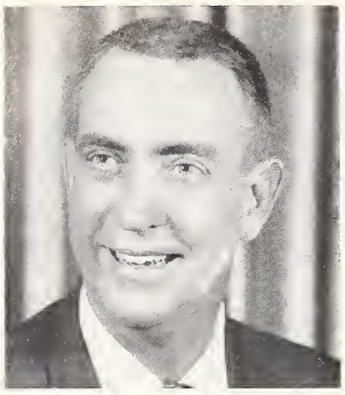


WILLIAM H. KERN
Chairman



DONALD L. BITTNER
Secretary

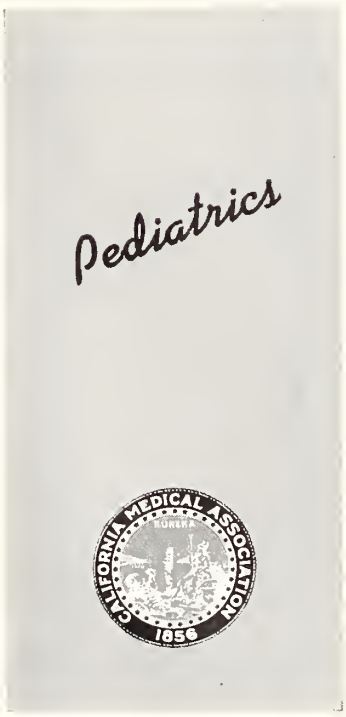




SHERROD C. SWIFT
Chairman



ROBERT J. HARVEY
Secretary



PEDIATRICS

Chairman SHERROD C. SWIFT, M.D., WHITTIER
Secretary ROBERT J. HARVEY, M.D., SAN FRANCISCO
Assistant Secretary EUGENE GETTELMAN, M.D., ENCINO

WEDNESDAY, MARCH 27 9:00 a.m.—Venetian Room Lobby Floor

Combined Meeting with Section on General Practice

9:00—**Introduction**—Sherrod C. Swift, M.D., Whittier.

9:05—**Basic Concepts of Viral Disease—Past and Present**—A. Frederick Rasmussen, M.D., Los Angeles, by invitation.

10:00—**The Immune Response of the Human With Particular Reference to Multiple Immunizations**—Paul F. Wehrle, M.D., Los Angeles.

10:50—**Recess.**

11:10—**Influenza and Other Viral Respiratory Infections**—Dorothy M. Horstmann, M.D., New Haven, Connecticut, by invitation.

12:15—**Business Meeting—General Practice.**

WEDNESDAY, MARCH 27 1:00 p.m.—Venetian Room Lobby Floor

Combined Meeting with Section on General Practice

1:00—**Recent Advances in Rubella**—Paul D. Parkman, M.D., Bethesda, Maryland, by invitation.

1:50—**Recent Concepts in Prevention and Immunization Against Viral Disease**—Samuel Baron, M.D., Bethesda, Maryland, by invitation.

2:40—**Recess.**

3:00—**The Laboratory Diagnosis of Viral Disease**—Speaker to be announced.

3:30—**Panel Discussion: Question and Answer Session.**

Moderator: Sherrod C. Swift, M.D., Whittier

Members of the Panel: A. Frederick Rasmussen, M.D., Los Angeles, by invitation; Paul F. Wehrle, M.D., Los Angeles; Dorothy M. Horstmann, M.D., New Haven, Connecticut, by invitation; Paul D. Parkman, M.D., Bethesda, Maryland, by invitation; and Samuel Baron, M.D., Bethesda, Maryland, by invitation.

4:00—**Business Meeting—Pediatrics.**

PHYSICAL MEDICINE

Chairman Anton A. Tratar, M.D., San Francisco
Secretary Elizabeth Austin, M.D., Los Angeles
Assistant Secretary C. Malvern Dorinson, M.D., San Francisco

MONDAY, MARCH 25 **9:00 a.m.—Vanderbilt Room Terrace Floor**

Combined Meeting with Section on Industrial Medicine and Surgery

9:00—**Thoughts on Rehabilitation**—Lorin L. Stephens, M.D., Arcadia.

9:45—**Recess.**

10:00— **Panel Discussion**

Is Physical Therapy Rehabilitation?

Moderator: Bernard J. Michela, M.D., Long Beach

Members of the Panel: Robert C. Geiger, M.D., Sonoma; Raymond O. Oja, M.D., San Francisco; William de la Joie, M.D., Los Angeles, by invitation; Donald E. Lamond, M.D., Stockton; and Royce P. Noland, R.P.T., Santa Cruz, by invitation.

12:15 p.m.—Garden Room Lobby Floor

12:15—**Luncheon and Business Meeting—Physical Medicine**—Advance reservations are necessary, and may be made with Sedgwick Mead, M.D., Kaiser Foundation Hospital, 2600 Alameda, Vallejo 94590, (707) 643-4551. Price: Approximately $5.50.

ATTENTION:

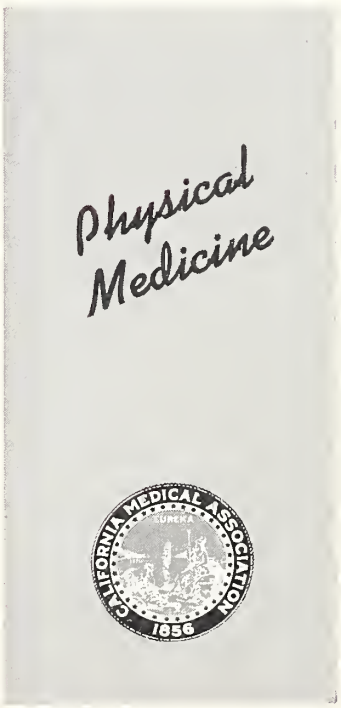
CHECK TELEVISION AND MOTION PICTURE PROGRAMS, PAGES 34-36



ANTON A. TRATAR
Chairman



ELIZABETH AUSTIN
Secretary





MAXWELL ROSENBLATT
Chairman



WILLIAM A. DEFRIES
Secretary



PREVENTIVE MEDICINE

Chairman MAXWELL ROSENBLATT, M.D., LOS ANGELES
Secretary WILLIAM A. DEFRIES, M.D., FRESNO
Assistant Secretary A. C. NEISWANDER, M.D., WHITTIER

TUESDAY, MARCH 26 **9:30 a.m.—Crystal Room Lobby Floor**

A Review of Comprehensive Health Planning

Chairman: Maxwell Rosenblatt, M.D., Los Angeles

9:30—**Comprehensive Health Planning — The National Scene** — James H. Cavanaugh, Ph.D., Bethesda, Maryland, by invitation.

9:50—**Comprehensive Health Planning at the Regional Level** — R. Leslie Smith, M.D., San Francisco, by invitation.

10:10—**Organized Medicine's Relationship to P. L. 89-749**—James C. MacLaggan, M.D., San Diego.

10:30—**Recess.**

10:40—**Hospitals and Their Relationship to Comprehensive Health Planning** — Samuel J. Tibbitts, Covina, by invitation.

11:00—**Comprehensive Health Planning — The California Version** — Lester Breslow, M.D., Los Angeles.

11:20—**Local Comprehensive Health Planning** — James C. Malcolm, M.D., Oakland.

11:40—**Panel Discussion and Questions from the Floor.**

12:00—**Business Meeting.**

MESSAGE CENTER

MESSAGE CENTER (415 781-4300)—*Provided through the courtesy of the Pacific Telephone and Telegraph Company* — Registration Desk, Main Lobby, Fairmont Hotel—Registration Desk is open from 8:00 a.m. until 5:00 p.m. — The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the convention number. Routine messages will be kept at the Message Center in the Fairmont Hotel Lobby.

Physicians are requested to check with the Message Center at least once a day.

PSYCHIATRY AND NEUROLOGY

Chairman AMES FISCHER, M.D., SAN FRANCISCO
Secretary HOWARD S. BARROWS, M.D., LOS ANGELES
Assistant Secretary HERBERT VANDERVOORT, M.D., SAN FRANCISCO

TUESDAY, MARCH 26 9:30 a.m.—Vanderbilt Room Terrace Floor

9:30—**Treatment of Myasthenia Gravis**—Christian Herrmann, Jr., M.D., Los Angeles, by invitation.
Discussion.

10:15—**Medical Treatment of Seizure Disorders**—Willard H. Pennell, M.D., San Francisco.
Discussion.

11:00—**Recent Developments in Psychopharmacology**—Leo E. Hollister, M.D., Palo Alto, by invitation.
Discussion and Question Period.

12:00—**Business Meeting.**

TUESDAY, MARCH 26 2:00 p.m.—Vanderbilt Room Terrace Floor

2:00—**Medical Treatment of Pain Syndromes, Especially Trigeminal Neuralgia**—Edward H. Davis, Beverly Hills.
Discussion.

2:45— **Panel Discussion**

Diagnosis, Evaluation, and Management of Acute Mental Syndromes in the Adult—Functional Psychosis Versus the Organic Brain Syndrome

Moderator: Ronald E. Saul, M.D., Los Angeles

Members of the Panel: Jerome Fisher, Ph.D., San Francisco, by invitation; and Jack H. Lindheimer, M.D., Rosemead.

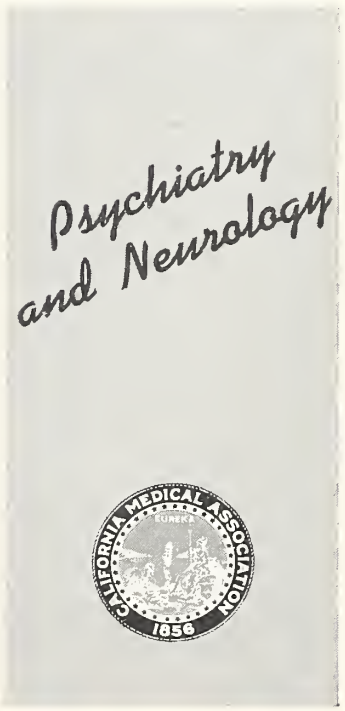
VISIT TECHNICAL EXHIBITS



AMES FISCHER
Chairman



HOWARD S. BARROWS
Secretary

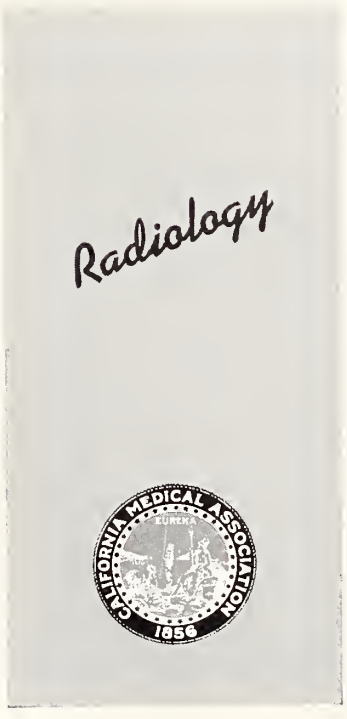




VERNON R. GEE
Chairman



RICHARD P. STORRS
Secretary



RADIOLOGY

Chairman VERNON R. GEE, M.D., REDDING
Secretary RICHARD P. STORRS, M.D., LOS ANGELES
Assistant Secretary H. JOACHIM BURHENNE, M.D., SAN FRANCISCO

SUNDAY, MARCH 24 **9:30 a.m.—Hunt Room Mezzanine**

9:30—**The Management of Patients with Nasopharyngeal Tumors**—Paul Y. M. Chan, M.D., by invitation; and Justin J. Stein, M.D., Los Angeles.

9:50—**Detection of the Zollinger-Ellison Syndrome: The Radiologist's Responsibility** — F. Frank Zboralske, M.D., Palo Alto, by invitation.

10:10—**Cystic Disease of the Kidneys in Children**—John L. Gwinn, M.D., Los Angeles.

10:30—**Business Meeting.**

Second Annual
L. Henry Garland Memorial Lecture

Sponsored by the California Radiological Society

11:00—**Introduction**—Saul Heiser, M.D., Los Angeles, President, California Radiological Society.

11:05—**The Present Status of Water-Soluble Contrast Media in the Examination of the Acute Abdomen**—Alexander R. Margulis, M.D., San Francisco.

SUNDAY, MARCH 24 **1:30 p.m.—Hunt Room Mezzanine**

1:30— **Clinico-Radiological Conference**

The Esophago-Gastric Junction

Moderator: H. Joachim Burhenne, M.D., San Francisco.

Members of the Panel: Orville F. Grimes, M.D., Howard A. Shapiro, M.D., San Francisco.

2:30—**Recess.**
2:45—**Annual Meeting of California Radiological Society.**

VISIT TECHNICAL EXHIBITS

UROLOGY

Chairman JAMES L. GOEBEL, M.D., SAN RAFAEL
Secretary ROBERT O. PEARMAN, M.D., ENCINO
Assistant Secretary . . MILTON ROSENBERG, M.D., SAN FRANCISCO

MONDAY, MARCH 25 **9:30 a.m.—Florentine Room Mezzanine**

9:30—**The Skin and Urologic Drug Problems** — John H. Epstein, M.D., San Francisco.

10:00—**Isotope Scanning Procedures — The New Look in Diagnosis**—Jerold M. Lowenstein, M.D., San Francisco.

10:30—**Newer Modalities in the Treatment of Wilm's Tumor**—Joseph H. Kushner, M.D., San Francisco.

10:50—**Chemotherapy and the Urologist**—Ernest H. Rosenbaum, M.D., San Francisco.

11:10—**Recognition of the "Bleeder"** — Ernest H. Rosenbaum, M.D., San Francisco.

11:30—**Clinical Observations on Kidney Tumors** — Miguel A. Llanos, M.D., Los Angeles.

11:45—**A Simple Technique for Ureteral Reimplantation**—Arjan D. Amar, M.D., Walnut Creek.

MONDAY, MARCH 25 **2:00 p.m.—Crystal Room Lobby Floor**

Combined Meeting with Section on Obstetrics and Gynecology

Alice Stone Woolley Memorial Lecture

Sponsored by the American Medical Women's Association

2:00—**The Association of Congenital Anomalies of the Urinary Tract with Abnormal Umbilical Cord Vessels and Chromosomal Patterns** — Edith L. Potter, M.D., Fort Myers, Florida, by invitation.

3:00—**Renal Hemodynamics and Sodium Excretion** — Charles A. Chidsey, III, M.D., Denver, Colorado, by invitation.

3:30—**Recess** — Urology Section to return to Florentine Room.

3:35 p.m.—Florentine Room Mezzanine Level

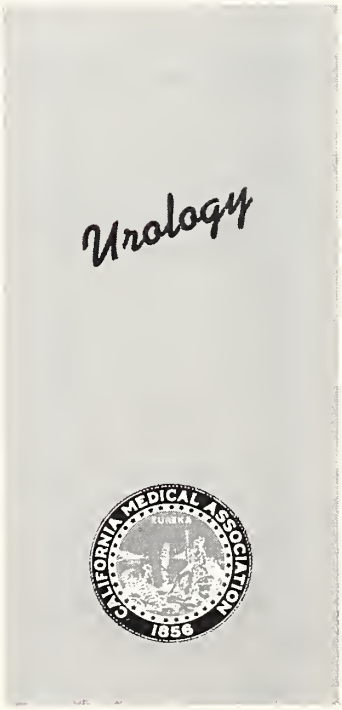
3:35—**Business Meeting.**



JAMES L. GOEBEL
Chairman



ROBERT O. PEARMAN
Secretary



TELEVISION PROGRAM

THE CALIFORNIA MEDICAL TELEVISION NETWORK

Selected Programs From
"This Moment in Medicine"
and
"Res Medica"

Terrace Room • Fairmont Hotel

PLANNED BY THE ADMINISTRATION AND PRODUCTION STAFFS OF THE HEALTH SCIENCES TELEVISION NETWORK, SAN FRANCISCO AND THE MEDICAL TELEVISION NETWORK, LOS ANGELES.

Seymour M. Farber, M.D., San Francisco
Donald W. Brayton, M.D., Los Angeles
A. Rodney Prestwood, M.D., San Francisco, by invitation
Richard S. Scott, M.D., Los Angeles, by invitation
Mr. Vern Louden, San Francisco, by invitation
Mr. Richard Getz, Los Angeles, by invitation

Videotapes of six recent presentations. Some of the participants and producers will be present to discuss programs and answer questions. General information about the California Medical Television Network (Videotapes), a cooperative educational project involving the medical communities of Northern and Southern California, will be presented.

MONDAY, MARCH 25 9:00 a.m.—Terrace Room
Terrace Floor

9:00— MODERN MOLECULAR GENETICS

Fundamental mechanisms of the genetic code in normal biology and in selected disease entities.

Produced by City of Hope Medical Center, Duarte.

Moderator: David E. Comings, M.D., Director, Department of Medical Genetics, City of Hope Medical Center, Duarte, by invitation.

10:15—**The California Medical Television Network.**

10:30— CONJOINED TWINS: SUCCESSFUL SEPARATION

Separation of thoracopagus twins and their status five years later.

Produced by Continuing Education in Health Sciences, University of California, San Francisco.

Moderator and participants to be announced.

11:45—**The California Medical Television Network.**

TUESDAY, MARCH 26 9:00 a.m.—Terrace Room
Terrace Floor

9:00— EARLY DETECTION OF UTERINE CANCER

Cytological specimen procurement procedures, pathology slides and specimens.

Produced by Continuing Education in Health Sciences, University of California, San Francisco.

Edward C. Hill, M.D., Associate Professor of Obstetrics and Gynecology, and Eileen B. King, M.D., Assistant Clinical Professor of Pathology, School of Medicine, University of California, San Francisco.

10:15—**The California Medical Television Network.**

10:30— SPORTS INJURIES—FOOTBALL

Live demonstrations of training techniques, preventive measures and injury management for the team physician.

Produced by University of California, Los Angeles, School of Medicine.

Moderator: Martin E. Blazina, M.D., Assistant Professor of Orthopedics, University of California, Los Angeles, School of Medicine.

Elvin Drake, Head Trainer, Department of Intercollegiate Sports, University of California, Los Angeles, by invitation.

11:45—**The California Medical Television Network.**

WEDNESDAY, MARCH 27

9:00 a.m.—Terrace Room
Terrace Floor

9:00— THE SUICIDAL PATIENT

Self-destructive urges in man: early clues and preventive techniques for the first-contact physician. Suicide as a medical and community responsibility.

Produced by University of Southern California School of Medicine and University of California, Los Angeles, School of Medicine.

Moderator: Robert E. Litman, M.D., Professor, Psychiatry, University of Southern California School of Medicine.

Norman L. Farberow, Ph.D., Associate Clinical Professor of Psychiatry, University of Southern California School of Medicine, by invitation; Ronald S. Mintz, M.D., Assistant Clinical Professor of Psychiatry, University of California, Los Angeles, School of Medicine; and Edwin S. Shnaidman, Ph.D., Chief, Center for Studies of Suicide Prevention, National Institute of Mental Health, Chevy Chase, Maryland, by invitation.

10:15—**The California Medical Television Network.**

10:30— CRISES IN DRUG USE:
YOUTH AND DRUG ABUSE

Pharmacology of illegal drugs used by youth, psycho-social factors, interviewing of drug users by physicians.

Produced by Continuing Education in Health Sciences, University of California, San Francisco.

John J. Antel, M.D., Director of Psychiatry, El Camino Hospital, San Jose; Ross De Boskey, M.D., Psychiatrist, San Francisco, by invitation; John I. Maurer, M.D., Staff Psychiatrist, Stanford University; James M. McKnight, M.D., Attending Staff, Marin General Hospital, San Rafael; and David E. Smith, M.D., M.S., Director, Alcohol and Drug Abuse Screening Unit, San Francisco General Hospital, by invitation.

11:45—**The California Medical Television Network.**

MOTION PICTURE PROGRAM

Terrace Room ■ Fairmont Hotel

Co-Chairmen:

Richard E. Gardner, M.D., San Francisco
W. Morris H. Noble, M.D., San Francisco

Three film symposia will be presented, each utilizing about two-thirds of the time for projecting of films, and one-third for discussion, questions and answers.

SUNDAY, MARCH 24 2:00 p.m.—Terrace Room Terrace Floor

2:00— Diagnosis and Management of Coronary Artery Disease

Moderators: Richard E. Gardner, M.D., and W. Morris H. Noble, M.D., San Francisco.

Discussants: Harold I. Griffeath, M.D., San Francisco; Edward J. Hurley, M.D., Davis; and Julius H. Grollman, Jr., M.D., Los Angeles, by invitation.

2:00—Introduction.

1. **Differential Diagnosis of Chest Pain**—Richard Ross, M.D., and G. C. Friesinger, M.D., Baltimore.

This film presents practical steps for the differential diagnosis of angina pectoris-like chest pain. The means for eliciting a meaningful patient history is introduced with lecture material and emphasized by dramatized physician-patient interviews. Relevant physical examination procedures and their rationale are discussed as is the relationship of angina pectoris to atherosclerosis and ischemic heart disease. The film is limited to diagnosis and does not touch on treatment either environmental or chemotherapeutic. 25 minutes.

2. **Myocardial Revascularization for Coronary Artery Disease** — Frank C. Spencer, M.D., and Edmund H. Reppert, M.D., New York City.

This film illustrates diagnostic coronary arteriography as developed by Doctor Sones at the Cleveland Clinic. Such studies are essential before planning any operative procedure for coronary artery disease. The operative procedures illustrated indicate implantation of the internal mammary artery, direct coronary endarterectomy, and implantation of the splenic artery. 34 minutes.

3. **Cine Coronary Arteriography** — F. Mason Sones, Jr., M.D., Earl Shirey, M.D., and Bernard V. Dryer, M.D., Cleveland.

This film is an introduction to normal and abnormal coronary artery structure as visualized by cine coronary arteriography. Part I demonstrates the selective catheterization of the left and right coronary arteries to visualize the human coronary artery tree, the wide range of normal anatomic variation in coronary artery distribution and the response of normal vessels to nitroglycerine. Part II shows some of the many varieties of pathology which may develop in the human coronary artery system and a few of the more frequently observed compensating patterns. 21 minutes.

3:45—Panel Discussion

Edward J. Hurley, M.D., Davis, Harold I. Griffeath, M.D., San Francisco, and Julius H. Grollman, Jr., M.D., Los Angeles, by invitation.

MONDAY, MARCH 25 2:00 p.m.—Terrace Room Terrace Floor

2:00— Drug Therapy

Moderator: To Be Announced.

2:00—Introduction.

2:05—**The Osteoporosis of Aging** — Richmond W. Smith, Jr., M.D., and Harold M. Frost, M.D., Detroit.

Current teaching techniques have been employed in this film to identify the osteoporotic process. Its nature is defined, its course determined and the latest treatment modalities presented. A review of normal bone development is presented in order to explain the nature of skeletal wasting. The remodeling process of bone and its regulators are discussed with regard to their role in the development of osteoporosis. Hormonal imbalance, calcium homeostasis, diet, mechanical stress, cellular aging and vascular alterations all may play a part in bone remodeling and subsequent osteoporosis. Current countermeasures that may slow or stop bone loss are presented. 20 minutes.

Discussion—Felix Kolb, M.D., San Francisco.

2:45—**Bacterial Meningitis** — Paul F. Wehrle, M.D., Los Angeles.

Concepts in the differential diagnosis and techniques of treatment of bacterial meningitis are discussed, as well as the complications associated with the disease. Also discussed are methods of treatment, including various forms of drug therapy. The disease is examined from the viewpoint of the problems faced by the practicing physician. 25 minutes.

Discussion—Richard Leonards, M.D., San Francisco.

3:30—To Be Announced.

(Continued on next page)

TUESDAY, MARCH 26 2:00 p.m.—Terrace Room Terrace Floor

2:00— Office Diagnostic Procedures

Moderator: Antonio Franzi, M.D., San Francisco.

2:00—Introduction.

2:05—**Oral Lesions in Children and Adults**—Howard Lewis, M.D., Portland, Oregon; Paul V. Woolley, Jr., M.D., Detroit; Carl Whitkop, D.D.S., Washington, D.C.; and Fred Henny, D.D.S., Detroit.

Fifty cases with typical lesions in both children and adults are shown in this film. These include infectious diseases, benign and malignant lesions, iatrogenic lesions and dental lesions. Techniques in examination are demonstrated on malignant lesions. Stress is given on prevention of permanent iatrogenic disorders. 28 minutes.

Discussion—Sol Silverman, Jr., D.D.S., San Francisco, by invitation.

2:55—**Office Management of Anorectal Lesions** — Raymond J. Jackman, M.D., and Clyde E. Culp, M.D., Rochester, Minnesota.

The film depicts thrombosed external hemorrhoid, injection treatment of internal hemorrhoids, rubber band treatment of internal hemorrhoids, anorectal abscess, pilonidal cyst, condyloma acuminata, polyps, pruritus ani, fecal incontinence, needle biopsy of prostate, rectal biopsy for amyloidosis, anal biopsy, and the use of dye in the diagnosis of rectovaginal fistula. 21 minutes.

Discussion—Walter D. Birnbaum, M.D., San Francisco.

3:35—**Office Diagnosis of Uterine Malignancy, Colposcopy, Cytology, and Biopsy** — Joseph W. Scott, M.D., Miami, and Carlos A. Vence, M.D., Detroit.

The film presents a new approach to the office diagnosis of uterine malignancy. In addition to the conventional methods of cytology and biopsy, it shows colposcopy, a technique of cancer detection not as yet widely used in this country. It then outlines the respective roles of colposcopy, cervical and endometrial cytology, and cervical and endometrial biopsy in the office diagnosis of uterine malignancy. 24 minutes.

Discussion—R. Elgin Orcutt, M.D., San Francisco.

REGISTRATION

Registration and information desks are located in the Main Lobby of the Fairmont Hotel. *All members, guests, and visitors are requested to register immediately upon arrival.* There is no charge for registration. Registration desks are open Saturday through Wednesday. *Admission to the general and section sessions, and exhibit area is by badge only.*

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

SCIENTIFIC AND ORGANIZATIONAL EXHIBITS

Grand Ballroom and Grand Ballroom Lounge, Fairmont Tower

Scientific Exhibits

Grand Ballroom, Fairmont Tower

Component Blood Therapy Means Better Patient Care —John A. Shively, M.D., Houston, Texas, and Charles Schulte, M.D., Arlington, Virginia, both by invitation. The exhibit's objective is to promote greater use of blood component therapy which, by its specificity, provides better patient care and conserves our human blood resources. The exhibit first presents the problem relating to the supply of and demand for these labile elements. Next, the methods developed and employed by the modern blood bank to make these blood components available are illustrated. Finally, practical guidelines for clinical usage are provided by the alignment of the specific components with their indications.

The Locomotor Function of the Pelvis — William S. Hunter, M.D., San Francisco. When strained, the obturator internus, piriformis, and coccygeus muscles may cause abdominal pain resembling appendicitis and other diseases, thereby leading to appendectomy or laparotomy. The models show the location of these muscles, and how they may be palpated. The evolution of the muscles is related to man's upright position, and the stress of this changed function helps explain the pathology seen in these muscles.

Localized Disorders of Ventricular Contraction — Bernard G. Krohn, M.D., Los Angeles. Cinefluorograms and electrical impedance cardiograms show that in various heart diseases defective contraction is limited to a portion of the ventricular wall. The exhibit will include prints from cinefluorograms showing ventricular dyssynergia (localized failures of the contraction of the ventricular wall). It will also include impedance cardiograms that record the same phenomena (in the same patients studied by cinefluorography). We also plan to exhibit an oscilloscope on which a vector impedance cardiogram will be continuously displayed from a magnetic tape recording of the heart motions of a patient.

Shock and Its Effect on the Cell—William Schumer, M.D., and Richard Sperling, M.D., Chicago, both by invitation. This exhibit shows that shock is a molecular disorder that concerns individual cells. It explains the anatomy of a cell and the function of each of its parts in relationship to this disorder. Normal cell biochemistry and energy demands are presented and these are compared with the changes that occur. A clear description is given of the metabolic derangements of shock and how these produce metabolic acidemia, cell malfunction and, at times, cell death. Recently, knowledge about these phenomena has advanced significantly. Today it is often possible to reverse the process of cell damage and death due to shock. Therapy is reviewed on the basis of modern-day, well-established concepts. The physician needs to understand the derangements that occur inside the molecules of a cell to more effectively control shock.

Chemotherapy of Metastatic Testis Cancer—A. Ranald MacKenzie, M.D., Robert B. Golbey, M.D., and Willet F. Whitmore, Jr., M.D., New York City, all by invitation. This exhibit reports the results of chemotherapy in 180 patients with metastatic testis cancer treated in Memorial and James Ewing Hospitals. A variety of agents have been used. The best results, however, have mainly been associated with programs which have included actinomycin D.

Scientific and Organizational Exhibits

Grand Ballroom Lounge, Fairmont Tower

Treatment of Ureteral Injury — Robert J. Prentiss, M.D., San Diego. A pictorial outline and explanation of the various types of surgical repair of ureteral injury.

Pathology of the Lung Related to Air Pollutants — William M. Blackmore, D.V.M., Hollywood, by invitation. The display consists of three sections divided into 13 window-type compartments containing photographs, diazo prints and real tissue sections of human and equine lung tissue in which conditions of adeno-carcinoma, bronchitis, and emphysema are demonstrated. Included in the display is an electron photomicrograph of the type of lung tumor found in mice exposed to Los Angeles air pollutants and some diazo prints of an emphysema-like condition found in rabbits, horses, and other animals.

California Committee on Regional Medical Programs — Paul D. Ward, San Francisco, by invitation. Four free-standing panels describing Regional Medical Programs in general terms, and from a national viewpoint, will be supplemented by additional information specifically describing programs planned by the eight medical schools, the California Medical Association and the California Hospital Association.

Recognition and Treatment of Hiatus Hernia—Howard C. Baron, M.D., and Leon Sasson, M.D., New York City, both by invitation. Hiatus hernia is demonstrable in 11 per cent of patients examined by gastrointestinal series. It is a common cause of dyspepsia, chest pain, and gastrointestinal bleeding. The disorder is frequently not recognized and a correct diagnosis is missed. Patients with symp-

(Continued on next page)

tomatic hiatus hernias are frequently considered psychoneurotic, hypochondriacal or functionally dyspeptic. Modern diagnostic techniques facilitate early diagnosis. Proper medical and surgical treatment can correct the pathophysiologic disturbances caused by the hernia. In this exhibit are presented etiologic factors, symptoms and recognition by radiographic, endoscopic, and pathophysiologic processes. The specific medical and surgical management is reviewed. The surgical procedure is illustrated with color transparencies of the operation supplemented by black and white line illustrations.

Hippocrates Revisited—Charles D. Willis, M.D., San Francisco, by invitation. Life of Hippocrates, history of Greek medicine, aphorisms and case histories of Hippocrates; mention of Imhotep, physician of Egypt; copy of oldest medical literature (Sumerian). Copy of Oath of Hippocrates will be available for handout.

Cryohypophysectomy in the Treatment of Diabetic Retinopathy—Nathan H. Roth, M.D., Pasadena, and Robert W. Rand, M.D., Los Angeles. This is a 15-foot exhibit with five panels showing criteria for selecting patients for cryohypophysectomy, contraindications, pictorial display of the operation and results on a select group of patients.

Physician-Nurse Communications — D. Ann Sparmacher, R.N., Chicago, by invitation. This exhibit represents a visual summary of the objectives and program of the American Medical Association Committee on Nursing. It emphasizes the importance of high standards of patient care through a close physician-nurse relationship. The areas of Liaison, Consultation, Research, and Education through which such a relationship can be strengthened are highlighted.

Pathology in Disorders of Hearing and Equilibrium—Francis A. Sooy, M.D., San Francisco. The pathology of disorders of hearing and equilibrium caused by measles, mumps, otosclerosis are shown. The technique for removal of temporal bones and their processing is described and illustrated.

University of Southern California Medical Alumni Association—Mrs. Bernice Kellar, Los Angeles, by invitation. A demonstration of the recent activities of the school, giving the available services for alumni and friends of the school.

Agnews State Hospital Research Program—Maurice Rappaport, M.D., San Jose. Results of basic and applied research projects will be displayed (Auditory Perception of Voice Messages in Schizophrenia, NAD Therapy in Alcoholism, and Signal Detection in Schizophrenia). In addition, a conceptual overview of a balanced research program will be presented along with the organizational structure of the research department. Views of the hospital and parts of the research program will also be presented.

WOMAN'S AUXILIARY

THIRTY-EIGHTH ANNUAL CONVENTION

MARCH 23 to 27, 1968

Headquarters: Fairmont Hotel, San Francisco

Convention Chairman: Mrs. Eugene S. Hopp

Convention Co-Chairman: Mrs. Lloyd Gillin

REGISTRATION: Fountain Room, Fairmont Hotel

Sunday, March 24—9:00 a.m. to 4:00 p.m.

Monday, March 25—8:00 a.m. to 4:00 p.m.

Tuesday, March 26—8:30 a.m. to Noon

SATURDAY, March 23

7:30 p.m.—Report to the CMA House of Delegates by Mrs. William R. Flood, Auxiliary President, Room of the Dons, Mark Hopkins Hotel. Doctors' wives are invited to attend.

SUNDAY, March 24

9:00 a.m.—Executive Committee Breakfast Meeting, President's Suite, Fairmont Hotel.

2:30 p.m.—Pre-Convention Board Meeting, 20th Century Room, Fairmont Hotel.

MONDAY, March 25

9:00 a.m.—Opening session of House of Delegates, Gold Room, Fairmont Hotel.

11:30 a.m.—Recess for Lunch.

2:00 p.m.—Afternoon Session of House of Delegates, Gold Room, Fairmont Hotel.

TUESDAY, March 26

9:00 a.m.—Final Session of House of Delegates, Gold Room, Fairmont Hotel.

12:30 p.m.—Presidents' Luncheon and Fashion Show, honoring Mrs. William R. Flood, Mrs. Robert J. Douds, Past State Presidents, CMA Advisory Board and wives. Elizabeth Arden Fashion Show, Gold Room, Fairmont Hotel.

WEDNESDAY, March 27

8:00 a.m.—Post-Convention Board of Directors Meeting, Mrs. Robert J. Douds, President, presiding, Fountain Room, Fairmont Hotel.

10:00 a.m.—Orientation Meeting for 1968-1969 State Board Members, Incoming County and District Presidents and Presidents-Elect, and interested Auxiliary members. Mrs. Robert J. Douds, presiding, Fountain Room, Fairmont Hotel.

HOSPITALITY CENTER—Fountain Room

Sunday, March 24—10:00 a.m. to 4:00 p.m.

Monday, March 25—9:00 a.m. to 4:00 p.m.

Tuesday, March 26—10:00 a.m. to Noon.



MRS. WILLIAM R. FLOOD, *President*



MRS. ROBERT J. DOUDS, *President-Elect*

Technical Exhibits

TECHNICAL EXHIBITS will be housed in the Fairmont Hotel's Grand Ballroom which may be reached from the Terrace Floor of the hotel or the California Street entrance to the Tower. Here the many exhibitors will present their products and services for members of the Association.

All exhibits and all products exhibited have been screened by a committee as a means of eliminating those which do not meet high standards. The exhibitors agree to this procedure and agree that by this means each will be in good company.

Here in one area will be found the latest developments in drugs, equipment and services to aid the physician in his professional activities. All physicians are urged to visit the exhibits; meetings have been planned to allow ample time for this important activity. Your visit will not only help bring your own knowledge up to date, but also, it will demonstrate to our exhibitors, who contribute so much to the success of the meeting, that we recognize and appreciate their fine cooperation.

Exhibits will be open from 9 a.m. to 5 p.m. each day, with an early closing on Wednesday.

ABBOTT LABORATORIES — Booth 103
North Chicago, Illinois

ACCOUNTRONICS — Booths 56 & 81
Los Angeles, California

ALOE DIVISION OF BRUNSWICK — Booth 40
St. Louis, Missouri

AMERICANA CORPORATION — Booth 7
Beverly Hills, California

ARMOUR PHARMACEUTICAL COMPANY — Booth 34
Chicago, Illinois

ARNAR-STONE LABORATORIES, INC. — Booth 51
Mt. Prospect, Illinois

AMERICAINE TOPICAL ANESTHETIC—20% dissolved benzocaine in a water-soluble base—ointment, suppositories and aerosol forms. Aerosol operates rightside up or upside down for contortion free application. HAZEL-BALM—cooling, soothing witch hazel and emollient lanolin in aerosol form—provides a comforting "cushion of foam." ISOCLOR—oral nasal decongestant and bronchodilator—tablet, liquid and timesule forms, also the anti-tussive Isoclor expectorant. SOPOR—Non-barbiturate hypnotic sedative for gentle untroubled sleep. Particularly useful with geriatric patients.

ASTRA — Booth 31
Worcester, Massachusetts

Information and descriptive literature pertaining to XYLOCAINE® (lidocaine) and CITANEST® (prilocaine) local and topical anesthetics, and iron preparations ASTRAFER® (dextriferron) for intravenous use and JECTOFER® (iron sorbitex) for intramuscular administration will be available at the ASTRA booth.

AUDIO-DIGEST FOUNDATION — Booth 52
Pacific Medical Equipment Co.
Los Angeles, California

AUDIO-DIGEST FOUNDATION (a non-profit subsidiary of the California Medical Association) gives the busy physician a time-saving tour through the best of some 600 current medical journals, plus the highlights of scores of national meetings. Time-proven, but still unique—these medical tape-recorded services are now offered in reel to reel tape and Phillips type cartridges—*General Practice, Surgery, Internal Medicine, Obstetrics & Gynecology, Anesthesiology, Ophthalmology* and *Pediatrics.*

Digest subscribers listen in their car, home or office. Carefully selected tape equipment for playing the Digests is offered at the convention by Pacific Medical Equipment Co.

AYERST LABORATORIES — Booth 5
New York, New York

AYERST LABORATORIES extends an invitation to visit our exhibit located in space #5 where ATROMID-S and PREMARIN are being featured. Our representatives will be pleased to discuss these or other AYERST products with you.

BANK OF AMERICA — Booth 29
San Francisco, California

BANK OF AMERICA'S PROFESSIONAL BILLING SERVICE is a computerized accounts receivable, billing and statistical service, designed to save the medical profession time and money. It provides attractive itemized statements and daily reports showing treatments, charges, payments and balances for each account. Complete with aged delinquency reports and treatment analyses (monthly), it also includes an annual account activity recap. PROFESSIONAL BILLING SERVICE is accurate, easy-to-use and assures control.

BEVERLY MEDICAL SUPPLY CO. — Booth 19
Beverly Hills, California

BEVERLY MEDICAL SUPPLY will show the latest instruments and equipment available from various major manufacturers. Emphasis will be on items to be used in the doctor's office.

BIOTRONICS, INC. — Booth 74
Redding, California

BIOTRONICS will exhibit the MACKAY-MARG ELECTRONIC TONOMETER. This instrument offers to the medical practitioner a modern answer to the problem of intraocular pressure measurement associated with older styles of tonometers. A typical examination takes less than three minutes. The easily interpreted tape, similar in appearance to an electrocardiogram, can be read by the doctor at his convenience. Because the measurement is quick, gentle, safe, free from the hazard of corneal abrasion, and permanently recorded, the actual measurements are generally done by a technician or office assistant.

BREON LABORATORIES, INC. — Booth 104
New York, New York

BREON LABORATORIES, INC. presents a full line of products for the care of patients with chronic obstructive pulmonary diseases. Included are ALEVAIRE, BRONKOMETER, BRONKOSOL, BRONKOTABS, BRONKOLIXIR and BRONKEPHRINE. Supplying a variety of formulas, dosage forms and actions; these products offer both prophylaxis and therapy, in chronic or acute conditions, to all ages. BREON personnel will gladly discuss specific products and therapies with you.

BRISTOL LABORATORIES Booth 1
Syracuse, New York

BURROUGHS WELLCOME & CO. Booth 68
Tuckahoe, New York

You are cordially invited to visit us for information on our products and the newest developments from the research facilities of Burroughs Wellcome & Co.

Of particular interest at this meeting is Zyloprim brand Allopurinol which represents a totally new concept for the management of gout, uric acid nephropathy and calculi, and hyperuricemia due to neoplastic disease and/or its intensive treatment.

Zyloprim was first synthesized in the Wellcome Research Laboratories in Tuckahoe, New York, and is the first drug to be marketed which reduces the formation of uric acid at its source.

CARNATION COMPANY Booth 9
Los Angeles, California

Carnation Company cordially invites you to visit Booth #9, where recent literature and information regarding Carnation Evaporated Milk, Carnation Instant Non-Fat Milk, Carnation Instant Breakfast and Carnation Slender are available.

Any question pertaining to our physician-researched material for use in your practice or hospital will be cheerfully discussed.

CASS & JOHANSING Booth 102
Los Angeles, California

Representatives will be present to discuss approved County Medical Association Programs—Group Disability, Non-Cancellable Disability, Life, and Accidental Death & Dismemberment.

In addition, assistance in complete insurance programming will be available.

CIBA PHARMACEUTICAL COMPANY Booth 67
Summit, New Jersey

Ciba Professional Service Representatives will be pleased to discuss Esimil.

COLE PHARMACAL COMPANY, INC. Booth 73
St. Louis, Missouri

Cole Pharmacal Company, Inc. will feature Iodo-Niacin® for use as a mucolytic and fibrolytic agent, Iso-Asminyl® for use in the acute asthmatic attack, and Asminyl® for more prolonged treatment. Banalg will be presented for use in gentle massage for minor aches and pains due to fatigue and overexertion.

CUTTER LABORATORIES Booths 37 & 38
Berkeley, California

Cutter *Display Booth — No. 37*

The role of human plasma fractions in hospital and private practice is demonstrated at the Cutter Laboratories' exhibit. New disposable syringe packaging of Hyper-Tet® will be featured. This human tetanus immune globulin is one of four hyper-immune gamma globulin fractions produced by Cutter. Added to these four are two other plasma fractions: Plasmanate®—a plasma protein product—and Parenogen®—a fibrinogen product.

Cutter *Hospital Display Booth — No. 38*

The Cutter Hospital Display Booth will illustrate the inherent safety advantages of the completely closed system feature in the famous Cutter line of Saftisystem I.V. administration sets and solutions. Sub-featured will be the expanding line of Cutter products for use with specialized medical procedures.

DAIRY COUNCIL OF CALIFORNIA Booth 13
Sacramento, California

Weighty Problems? Resource and reference data for doctors, and information to be used with patients concerning weight control. Basic materials about normal food needs for all age groups also are provided without charge.

DAYLIN MEDICAL & SURGICAL SUPPLY, INC. Booth 18
Los Angeles, California

DOME LABORATORIES Booth 98
New York, New York

Our trained representatives will be on hand to discuss our dermatological specialty products with you, including our ultra-violet sunscreen lotion—Uval—and Micronaire, our new room purifier that cleanses the air by electrostatic precipitation. We look forward to having you as our guest.

DONOVAN HERSHEY CORPORATION Booth 94
Los Angeles, California

Code-A-Phone automatic answering equipment—the only goof-proof answering service that doctors are using more and more. Maintains your professional and personal doctor-patient relationship. Code-A-Phone answers every call with your voice, answers promptly, never puts a caller on "hold," cannot make a mistake, and never garbles a message. Remote control "key" allows you to receive your calls from anywhere. Fully approved by the telephone company for connection. You keep the personal touch your patients appreciate with Code-A-Phone. Code-A-Phone is on duty all the time—you can screen out those calls you wish to return. See an interesting demonstration at the exhibit.

ENCYCLOPAEDIA BRITANNICA, INC. Booth 100
Chicago, Illinois

Encyclopaedia Britannica and its publications welcomes all delegates to the 1968 California Medical Association annual session and invites them to examine the great new editions of Britannica.

Official delegates may now purchase this magnificent set at an offer only available at our convention exhibits. Visit Britannica's Booth Number 100.

ENDO LABORATORIES, INC. Booth 72
Garden City, New York

Endo Laboratories will present the latest clinical information relating to our products, Coumadin® (sodium warfarin), Numorphan® (oxymorphone) HCL, Percodan®, Percodan®-Demi, Hycomine®, Hycomine®-Compound, Hycodan®, Valpin® (anisotropine methylbromide), Valpin®-PB (anisotropine methylbromide with phenobarbital).

CHARLES O. FINLEY & CO., INC. Booth 4
Los Angeles, California

California Medical Association Disability Insurance Program.

FLINT LABORATORIES Booth 32
Division of Travenol Laboratories, Inc.
Morton Grove, Illinois

Featured will be FLINT LABORATORIES' newly introduced CHOLOXIN® (sodium dextrothyroxine) which effectively lowers elevated serum cholesterol. Also featured will be HU-TET® (tetanus immune globulin, human), the homologous tetanus antitoxin and SYNTHROID® (sodium levothyroxine) indicated in hypothyroidism.

FULLER LABORATORIES, INC. Booth 59
Eden Prairie, Minnesota

The "TUCKS family of products," TUCKS medicated pads, TUCKS TAKE-ALONGS, TUCKS witch hazel Ointment and Cream, for management of pruritus ani, hemorrhoidal, and perineorrhaphy discomfort.

THERAPADS, therapeutic aid for complexion problems.

FULLER SHIELD, a dressing used following anorectal and pilonidal surgery, and its companion A.R.D. butterfly-shaped dressing.

SCOPETTES, proctosigmoidoscopic swabs. Lint free, holds shape wet or dry.

GEIGY PHARMACEUTICALS Booth 36
Ardsley, New York

GEIGY PHARMACEUTICALS cordially invites members and guests of the association to visit its exhibit. The exhibit features important new therapeutic developments in the management of cardiovascular disease as well as current concepts in the control of inflammation: hypertension and edema; depression; obesity, and other disorders, which may be discussed with representatives in attendance.

J. H. HEDRICK CO. Booth 12
South San Francisco
Santa Barbara
San Gabriel
San Diego, California

C-Planning, Design, Plans, Financing & Construction of Med-Dental Bldgs. & Conv. Hospitals.

HOTCHKISS INSTRUMENTS Booth 92
Corte Madera, California

KNOLL PHARMACEUTICAL COMPANY Booth 101
Orange, New Jersey

AKINETON Parkinson's/drug induced extrapyramidal disorders. DILAUDID acute and chronic pain. DILAUDID COUGH SYRUP for fatiguing non-productive cough. METRAZOL, VITA-METRAZOL, and NICO-METRAZOL in treatment of geriatric patients for relief of symptoms of senility, apathy and chronic fatigue. QUADRINAL and VEREQUAD for relief of bronchospasm and wheezing. Introducing our *new* bronchodilator/expectorant THEOKIN ELIXIR for the symptomatic treatment of bronchial asthma, chronic bronchitis and pulmonary emphysema.

LEDERLE LABORATORIES Booth 69
Division of American Cyanamid Co.
Pearl River, New York

LEDERLE LABORATORIES is proud to support the 1968 Annual Session of the California Medical Association. As one of the leaders in medical research and quality controlled production, we present for your consideration products such as DECLOMYCIN® (demethylchlortetracycline HCL), ACHROMYCIN®V (tetracycline), ARISTOCORT® (triamcinolone), LEVOPROME® (methotrimeprazine) DECLOSTATIN® 300 (demethylchlortetracycline and nystatin), MYAMBUTOL (ethambutol HCL), and others applicable to your practice. Our representatives in Booth No. 69 are also prepared to provide information on our numerous services to medicine.

ELI LILLY & COMPANY Booth 35
Indianapolis, Indiana

You are cordially invited to visit the LILLY exhibit. Our sales representatives in attendance will welcome your questions about LILLY products. You may be particularly interested in discussing V-CILLIN K® Potassium Phenoxymethyl Penicillin.

LOMA LINDA FOODS Booth 26
Riverside, California

LOMA LINDA FOODS, one of America's oldest manufacturers of fiber-free hypo-allergenic infant soy milk, will show evidence of the nutritional adequacy of the product SOYALAC. Representatives will explain why it is unusual in that it does not settle out, is milk-like in texture, and does not tend to raise infants' serum cholesterol. Uses for adult ulcer patients and in cholesterol-lowering diets will be discussed. Samples will be served and recipes presented indicating the versatility of the product in diets of those with milk allergies or who for other reasons need to eliminate dairy milk from the diet.

LUXO-LAMP CORPORATION Booth 76
San Francisco, California

Incandescent, Fluorescent, Color-Corrected examination and minor surgical lamps on flexible arms, spring balanced to hold in any position, with reach up to 60″ from mounting. Illuminated Magnifiers for critical inspection, foreign matter removal, stitching, etc. Universal brackets available for attaching to equipment or separate mounting in any location. Also Patient Room Lighting units including General Illumination, Night Light, and combination Reading and Doctor's Examination Lamp.

MEAD JOHNSON LABORATORIES Booth 45
Evansville, Indiana

The MEAD JOHNSON LABORATORIES' exhibit has been arranged to give you the optimum in quick service and product information. To make your visit productive, specially trained representatives will be on duty to tell you about their products.

MEDICAL MANAGEMENT CENTER Booth 96
San Francisco, California
Los Angeles, California

Management Consultants to the medical profession specializing in:
Partnership Formation and Operation.
Office Management, Systems and Procedures.
Taxes and Tax Planning.
Net Worth Growth Planning.
Facilities Expansion and Construction Planning.
Member: Society of Professional Business Consultants
Association of Management Consultants
American Management Association

MERCK SHARP & DOHME — Booth 41
West Point, Pennsylvania

The Merck Sharp & Dohme exhibit has been designed to supplement the physician's therapeutic armamentarium. Technically trained personnel are present to discuss the scope and variety of services offered.

MILEX-WESTERN CO. — Booth 50
Los Angeles, California

"Milex" and "Office Gynecology" are synonomous. "Milex" and "Patient Counseling Books" are synonomous. Come and see the latest instruments used in office gynecology. Come and see the latest books used in patient counselling.

THE NETTLESHIP COMPANY OF LOS ANGELES — Booth 25
Los Angeles, California

Administrators of Professional Liability, Group Accident & Sickness, and Life Insurance Programs for County Medical Associations & Trusts in California.

Qualified representatives available to discuss problems pertaining to hospital or individual professional liability coverage, accident and sickness, life, or other types of insurance.

Literature which will assist in the prevention of claims and various forms to be used to protect, as far as possible, against malpractice claims.

NEUTROGENA CORPORATION — Booth 48
Santa Monica, California

Non-medicated Neutrogena is a safe, mild, thorough cleanser that does nothing but clean. Unusual cleansing action lessens usual defatting and irritating characteristics of cleansers. (U.S. Patent No. 2820768.) Whatever the etiology of a dermatosis this transparent, ethanolamine base soap is well tolerated in the cleansing care of subsequent cutaneous irritation and inflammation.

NIAGARA THERAPY MANUFACTURING CORPORATION — Booth 91
San Francisco, California

ORGANON, INC. — Booth 6
West Orange, New Jersey

Hexadrol dexamethasone offers brand-name quality at economy prices in tablets, injectable, elixir and cream form. New diagnostics Monosticon—with its new blue end point, Rheumanosticon—a one-minute slide test to detect rheumatoid factor, and Pregnosticon Slide Test for HCG levels in pregnant urine, are also featured.

ORTHO PHARMACEUTICAL CORPORATION — Booth 8
Raritan, New Jersey

PARKE, DAVIS & COMPANY — Booth 75
Detroit, Michigan

You are cordially invited to visit the Parke, Davis exhibit which features two new products—Norlestrin® 1 mg. (each tablet contains norethindrone acetate 1 mg. and ethinyl estradiol 0.05 mg.) and Ponstel® (mefenamic acid).

P.P.S. — Booth 88
San Mateo
San Francisco, California

The most complete electrical bookkeeping and billing service available. This service was designed by doctors for the medical profession. It includes filling out insurance claim forms, both on an automatic and callup basis. Complete summaries of all transactions are supplied, and a depository may be used for daily deposits made directly to your bank account.

PFIZER LABORATORIES — Booth 15
New York, New York

PHARMACIA LABORATORIES, INC. — Booth 46
Piscataway, New Jersey

Pharmacia Laboratories, Inc. (Originators of the Dextrans) will exhibit their dextrans: Rheomacrodex (dextran 40), also known as low molecular weight dextran; Macrodex (dextran 70), known as clinical dextran; and Azulfidine (salicylazosulfapyridine) "the mainstay of therapy" for each and every stage of ulcerative colitis, plus Azulfidine En-Tabs (enteric-coated Azulfidine).

PITCHER ELECTRONICS — Booth 28
Brea, California

Siemens equipment will be featured.

WM. P. POYTHRESS & CO., INC. — Booth 64
Richmond, Virginia

The Poythress exhibit will feature Trocinate, a unique direct-acting (musculotropic) antispasmodic drug, and the Mudrane combinations, established Poythress products for relief of bronchial asthma. Solfoton, Solfo-Serpine, Panalgesic and Synirin will also be featured. Your requests for literature and professional trial quantities are cordially invited.

RITTER EQUIPMENT COMPANY — Booth 11
Division of Ritter Pfaudler Corporation
Rochester, New York

Ritter invites you to its booth to see the new decorator colors—finish and fabric—now available in connection with its fully-powered "75" Table and Mobilrest Stool. Also available in new decorator finish are the No. 8 Light, No. 7 SpeedClave, Bantam Bovie and the recently introduced Ritter Coagulator. This latter product is a most important addition to the line and one that can prove extremely useful in your treatment rooms. Also see the Ritter XL45 Table featuring power elevation with adjustable back and seat sections. Meet your friends at the Ritter booth and see these quality products on display.

A. H. ROBINS COMPANY — Booth 71
Richmond, Virginia

You are cordially invited to visit the Robins display and meet our representatives who will welcome the opportunity to discuss products of interest with you.

ROCHE LABORATORIES — Booth 39
Nutley, New Jersey

Continuing Roche research has produced outstanding contributions to medicine since 1909. The personnel at the exhibit welcome your comments, questions or suggestions about our products and services.

SANDOZ PHARMACEUTICALS — Booth 43
Hanover, New Jersey

Sandoz Pharmaceuticals cordially invites you to visit our display at Booth #43 where we are featuring Mel-

LARIL, SANSERT, CAFERGOT P-B, FIORINAL and FIORINAL with codeine.

Any of our representatives in attendance, will gladly answer questions about these and other SANDOZ products.

W. B. SAUNDERS COMPANY — Booth 44
Philadelphia, Pennsylvania

SAUNDERS will have on display a complete line of their medical books, including many new titles and new editions, such as—Ballinger et al: The Management of Trauma; Conn: Current Therapy 1968; Gellis and Kagan: Current Pediatric Therapy, III, and many others.

SCHERING LABORATORIES — Booths 3 & 58
Union, New Jersey

SCHERING CORPORATION invites you to visit their Self Service Area, Booth Space No. 58, where practice and teaching aids are available on request and the SCHERING MEDICAL SLIDE LIBRARY will be on display.

THE SCHOLL MANUFACTURING CO., INC. — Booth 16
Chicago, Illinois

Registered nurses and other trained sales representatives will be available to demonstrate the techniques of tubular gauze bandaging with TUBEGAUZ products. In addition, other products on display will include DECUBINIX HEEL and ELBOW PROTECTORS, DECUBINIX BED PADS, "one-patient use," REUSABLE PLASTIC ICE BAGS and the new DECUBINIX SPLINT LINER for use with posterior tibia and fibula aluminum splints.

G. D. SEARLE & CO. — Booth 2
Chicago, Illinois

You are cordially invited to visit the SEARLE booth where our representatives will be happy to answer any questions regarding SEARLE Products of Research.

Featured will be information on OVULEN-21, ENOVID, ALDACTAZIDE, FLAGYL, LOMOTIL, PRO-BANTHINE and other drugs of interest.

SICULAR X-RAY CO., INC. — Booth 78
San Francisco, California

ULTRASONIC LAMINOGRAPH complete with oscilloscope camera, contour scanner with articulated transducer support and electronic position computer for use in measurement of the location of the mid-line of the brain, time and motion studies of the micro valve detection of fetal heartbeat and many other aspects of pregnancy, identification of hydatid moles, fibroid tumors, etc.

PICKER POLAROID SYSTEM which is a complete self-contained system for 45 second processing of a positive radiographic image on polyester requiring considerably reduced levels of radiation exposure. The radiographic exposure is dry processed in a portable processor without the need of darkroom, solutions, or dryer. The translucent image can be read on standard x-ray illuminators.

SIEMENS MEDICAL OF AMERICA, INC. — Booth 27
Addison, Illinois

SIEMENS MEDICAL will display many advancements in diagnostic and therapy equipment. Our representatives will be on hand to demonstrate our equipment and discuss practical applications with you. We believe a few minutes at our booth will prove to be well spent.

SMITH, KLINE & FRENCH LABORATORIES — Booth 47
Philadelphia, Pennsylvania

Featured will be our comprehensive oral diuretic, DYAZIDE, each capsule containing 50 mg. of Dyrenium (brand of triamterene) and 25 mg. of hydrochlorothiazide.

SMITH, MILLER & PATCH, INC. — Booth 60
New York, New York

SMITH, MILLER & PATCH, INC. will appreciate the opportunity to discuss with you the latest clinical reports concerning LIPOFLAVONOID; our recently enlarged line of hematinic tablets, VITRON, VITRON-C and VITRON-C PLUS; many new ophthalmic products; and our new NASOCON NASAL SPRAY. KONDREMUL and LIPOTRIAD will also be featured.

E. R. SQUIBB & SONS — Booth 33
New York, New York

STACEY'S — Booth 105
Palo Alto, California

Medical books of all publishers.

STUART DIVISION — Booth 70
Atlas Chemical Industries, Inc.
Pasadena, California

A cordial invitation is extended to all members and guests attending this meeting to visit the STUART DIVISION-ATLAS CHEMICAL INDUSTRIES, INC. booth. Specially trained representatives will be in attendance to answer your questions on new products developed in our modern laboratories, which have particular interest for the medical profession. Products featured are DIALOSE®, DIALOSE® PLUS, MULVIDREN®, MULVIDREN®-F, MYLANTA®, MYLICON®, STUART PRENATAL®.

SUREL INC. — Booth 24
Philadelphia, Pennsylvania

SUREL, a subsidiary of SMITH KLINE & FRENCH LABORATORIES, will feature its extensive line of absorbable and nonabsorbable surgical sutures, including specialties in surgical gut, braided silk, braided Dacron, monofilament nylon and monofilament stainless steel. Our representatives will be pleased to show you samples of our products and discuss their application to your practice. They will also be happy to arrange for complimentary trial supplies of items you may wish to evaluate under clinical conditions; and to tell you about our other services to physicians and hospitals.

SYNTEX LABORATORIES, INC. — Booths 17 & 42
Palo Alto, California

SYNALAR® (fluocinolone acetonide), the topical corticosteroid designed to meet specific dermatologic needs, will be featured at Booth 17. SYNALAR has set a new standard of success in the treatment of a wide range of inflammatory dermatoses.

A warm invitation is extended to all physicians attending this meeting to visit our booth and discuss the latest developments from SYNTEX research.

NORINYL®-1 (Norethindrone 1.0 mg. with mestranol 0.5 mg.) tablets an original steroid from SYNTEX LABORATORIES, will be featured at Booth 42. NORINYL-1 provides

effective fertility control on half the previous dosage.

Physicians are invited to register at the SYNTEX exhibit for complete information on this outstanding product.

SYSTEMEDICS, INC. Booth 30
San Francisco, California

SYSTEMEDICS, INC. medical office systems for billing, credit letter follow up and insurance form preparation. The SYSTEMEDICS system virtually eliminates bookkeeping chores in the medical office. It provides accurate, detailed statements, insurance reports and information for general management purposes. The entire operation can be handled by one individual, with a minimum of time and effort, with no equipment involved.

3M CO. BUSINESS PRODUCTS SALES INC. Booth 77
Santa Clara, California

Statement machine and accessory equipment for sending monthly statements. Also copying equipment for all types of reproduction work in large or small office.

THE UPJOHN COMPANY Booths 65 & 66
Kalamazoo, Michigan

Professional representatives of THE UPJOHN COMPANY are eager to contribute to the success of your meeting. We are here to discuss with you products of UPJOHN research that are designed to assist you in the practice of your profession. We solicit your inquiries and comments.

DEAN WITTER & COMPANY Booth 61
San Francisco, California

DEAN WITTER & CO. proposes to have an investment information booth staffed by personnel who are equipped to inform members of your Association about the financial services available by DEAN WITTER & Co., and specifically assist your physicians about provisions of the Keogh Bill.

WYETH LABORATORIES Booth 63
Philadelphia, Pennsylvania

REGISTRATION

Registration and information desks are located in the Main Lobby of the Fairmont Hotel. *All members, guests, and visitors are requested to register immediately upon arrival.* There is no charge for registration. Registration desks are open Saturday through Wednesday. *Admission to the general and section sessions, and exhibit area is by badge only.*

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

OFFICERS AND DELEGATES

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House of Delegates

TOTAL DELEGATES (342)

DELEGATES EX-OFFICIO (71)

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Malcolm C. Todd, Long Beach President-Elect
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Joseph F. Boyle, Los Angeles Vice-Speaker, House of Delegates
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Malcolm S. M. Watts, San Francisco Editor

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Richard S. Wilbur (1970) Office No. 1, Seventh District
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°Albert G. Clark (1969) Office No. 1, Eighth District
Roberta Fenlon (1970) Office No. 2, Eighth District
Harold Kay (1969) Office No. 1, Ninth District
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James H. Yant (1968) Eleventh District
Forest J. Grunigen (1970) Twelfth District
William P. Longmire, Jr. (1968) .. Scientific Board Representative

°Council Appointees.

ELECTED DELEGATES (271)

Delegates	*Alternate*
ALAMEDA-CONTRA COSTA (20)	
Ackerman, Frederick	Adams, Robert
Anderson, Conrad E.	Barber, Thomas E.
Armstrong, James R.	Barron, Gilbert
Black, Daniel W.	Bassett, J. Brandon
Boysen, Edwin E.	Byers, Gilbert
Davis, Aaron E.	Cohen, James I.
Donald, William G., Jr.	Duffy, Charles C.
Eisenberg, Harold J.	Frost, Gordon
Hart, Charles J.	Goetsch, Carl
Holden, Herbert	Greist, Elwood C.
Hoskins, H. Dean	Juul, Clement O.
Hudson, Charles B.	Kirk, Ralph
Kunkel, Peter	Martin, L. Robert
Lewis, Gwilym B.	Miller, A. Donald
Powell, Oscar M.	Morrison, J. Evans
Purcell, Edward F.	Plaut, Eric A.
Richards, Dexter N.	Reedy, Richard N.
Rihn, Richard J.	Ross, Joseph
Truman, Stanley R.	Thompson, Preston G.
Twigg, Edward	Wiesinger, Warren E.
BUTTE-GLENN (2)	
Elmendorf, Thomas	Chiapella, William C.
Murphy, Franklin L.	Ritter, Dale W.
FORTY-FIRST (2)	
FRESNO (5)	
Argo, W. L.	Ginsburg, H. M.
Howard, Arthur F.	Kirkegaard, Dale
Kass, Robert	Millar, Max S.
Smith, Robb	Steinberg, Theodore
Snyder, L. J.	Wilde, N. John
HUMBOLDT-DEL NORTE (2)	
Loring, Theodore	Braafladt, H. J.
Smith, E. Kenneth	Bux, Donald E.

Delegates	*Alternate*
IMPERIAL (2)	
Jaquith, George	Ajalat, M. P.
Schoensee, Burke	La Chance, Raymond D.
INYO-MONO (2)	
Alm, Theodore E.	Christenson, Donald L.
Denton, Robert W.	Jones, Milton R., Jr.
KERN (4)	
Day, Robert L.	Anderson, Gene
Osell, L. N.	Clark, M. Marlin
Strongin, Seymour	Reese, Thomas V.
Vaughan, J. E.	Spaulding, Keith W.
KINGS (2)	
Brookshier, R. W.	Barreiro, A. L.
Kerr, Edwin E.	Bean, Glenn M.
LASSEN-PLUMAS-MODOC-SIERRA (2)	
Bross, Willard S., Jr.	Batson, Wilbur C.
Quinn, William J.	Korver, Kenneth G.
LOS ANGELES (90)	
Adams, Donald A.	Alexakis, Peter
Alter, Marvin S.	Anderson, James E.
Andersen, George C.	Anderson, Richard E.
Asher, Leonard M.	Barker, Donald E.
Austin, R. Reed	Blake, Courtland A.
Axelrod, Bernard	Bernstein, Harold

Delegates	*Alternate*
LOS ANGELES (Continued)	
Bailey, Wilbur	Bleecker, Harry H., Jr.
Barber, Clifford A.	Botzbach, Henry A.
Beasom, Ralph D.	Brennan, John C.
Blood, William	Bruckner, Sherman H.
Bowen, Gordon T.	Casberg, Melvin A.
Boyle, Joseph F.	Cobb, Dudley M., Jr.
Buehler, George S.	Cobley, George G.
Bullis, John A.	Coleman, Thomas J.
Bullock, Lewis T.	Del Junco, Tirso
Campion, George M.	Dickerson, Donald E.
Case, Walter G.	Dotson, Christopher G., Jr.
Compton, Russell F.	Erickson, James F.
Cope, Jerome A.	Feinberg, Munish
Crane, Jay J.	Feldman, David H.
Crum, Jean F.	Fife, J. Kingsley
Donahue, D. W.	Fischer, Barton L.
D'Orazio, Edward	Fox, Saul L.
Dorn, Robert M.	Freeman, Gordon L.
Dummer, Jerome M.	Freidin, Morris
Ellerbeck, Walter P.	Frick, William Oliver
Elshire, H. Donel	Furer, Stanford A.
Evans, Creed M.	Gates, Earl F.
Evashwick, George	Goldstein, David
Fields, Albert	Goodwin, William E.
Fitch, Donald R.	Greco, Donald J.
Florea, Darwin	Hardin, Byron
Ford, James H.	Hoffman, Peter L.
Fox, James B.	Horton, James W.
Fredericks, Robert E.	Howard, Sidney M.
Gondek, Frank R.	Hull, Forrest E.
Halasey, Thomas	Husted, Russell M.
Hamel, Neal C.	Kaspar, Friedrich H.
Haskell, M. M.	Kaufmann, Bertram J., Jr.
Hill, Harry E.	Kearns, Walter M., Jr.
Hoffman, Eugene F., Sr.	Kelley, Walter W.
Hohl, Mason	Kern, William H.
Hood, Robert T., Jr.	Korn, Bernard J.
Horner, David B.	Lefevre, Timothy M.
Jacobs, Laurence L.	Lopez, Charles J.
Jones, Henry A.	MacKenzie, Ronald J.
Keltner, Mark R.	Martin, Walter P.
Kessler, Bruce J.	McCandless, Harrison
Ketcham, Burton E., Jr.	McCleary, Jack E.
Kiddie, Thomas	McElwee, Charles B.
Kranzdorf, Charles D.	McLaughlin, Henry M.
Lau, Michael W.	Medler, David C.
MacInnis, Douglas N.	Meine, Emile L., Jr.
Mailman, Richard H.	Michels, Arthur G.
Mauer, Edgar F.	Miller, Woodrow
May, Lewis H. V.	Mueller, Robert L.
Miller, Richard D.	Nishizawa, Akira
Milliken, Ralph M.	Odou, Eugene R.
Morgan, Frank M.	Olch, David
Morgan, Henry G.	Palmer, Robert H.
Murray, Gregory C.	Penka, Ernest J.
Murrieta, A. J., Jr.	Penn, Sidney
Neuenschwander, Robert S.	Picklesimer, James C.
Nippell, Robert M.	Rabens, Robert A.
Ottalini, Guy Adams	Rago, Marco R.
Parlour, Richard R.	Rayman, Irving B.
Payne, J. Howard	Reeder, David H.
Phares, Walter S.	Rudy, Norman E.
Pheasant, Homer C.	Ryerson, F. Stuart
Pollack, John V.	Silver, Bernard B.
Quinn, William F.	Smiley, Douglas F.
Richards, Melvin	Stauffer, Floyd R.
Rogers, Frank A.	Stout, Carlyle F.
Rothenberg, Sanford F.	Sullivant, Richard A.
Smith, Seth Willard	Summers, L. F.
Smith, Thayer A.	Tashma, Albert
Starr, Harvey E.	Taylor, William A.
Stragnell, Robert	Thom, John G.
Taw, Richard L.	Tudbury, Patricia B.
Trumbull, William E.	Turrill, Fred L.
Wagner, Joseph	Veregge, Gerald S.
Wasserman, John M.	Vogel, Philip J.
Watson, Robert L., Jr.	Walter, LeRoy E.
Weber, Robert A.	Weiss, Murray J.
Westerbeck, Charles W.	Wigton, John R.
Whipple, Winston	Wong, Thomas A.
Wiater, Edward J.	Woolley, Morton M.
Woolington, Sam S.	Wright, Carter R., Jr.
Yates, Paul D.	Wunderlich, E. E.
Zinn, Willard J.	
MARIN (3)	
Ablin, Arthur R.	Alderson, Joseph J.
McGee, John	Raney, Gus
Weden, Elmer A.	White, A. Halnan
MENDOCINO-LAKE (2)	
Roberson, B. B.	Nicholson, Thomas A.
Smalley, Robert B.	Waring, William
MERCED (2)	
Anglin, John V.	Corbett, Thomas
Udall, Addison R.	Soderstrom, Edwin

Delegates	*Alternate*
MONTEREY (3)	
Hull, Osman H.	Eldredge, Eugene E.
Klinefelter, Robert P.	Kandlbinder, A. F.
Turner, Joseph E.	Pulford, James H.
NAPA (2)	
Brignoli, Walter H.	Ashley, Robert C.
Ledwich, Thomas W.	Ehrlich, Harry
ORANGE (13)	
Altman, Richard F.	Bouchelle, McLemore
Ball, Dexter T.	Burrill, C. William
Carroll, Vincent P.	Donaldson, A. Norton
Gerrie, Wallace A.	FitzGerald, P. J.
Graham, Ralph E.	Geddes, David K.
Hawkins, G. William	Hastings, Charles M.
Jett, Jim	Kammerman, Richard F.
Kay, Fred M.	Martin, Walter H.
Mosier, Laurance A.	Nielsen, David I.
Paul, Carl J.	Plows, Charles W.
Plumb, Hugh J., Jr.	Schneider, Shirley M.
Price, J. B.	Siemonsma, Harry L.
Stonestreet, Marshall	Thompson, Arthur F.
PLACER-NEVADA (2)	
Morgan, D. L.	Chargin, J. E.
Shamhart, H. William	Dubin, Nathan
RIVERSIDE (5)	
Abbott, Donald	Borak, Peter J.
Ivanoff, John C.	Kinney, William
Jones, Cecil	Lyons, John C.
Stone, H. H.	Pitchford, Clyde A.
Zweig, Robert M.	Silver, Harrison E.
SACRAMENTO (8)	
Berg, John A.	Babich, John
Berman, A. E.	Fong, William
Cook, Orrin S.	O'Kane, Calvin R.
Farley, James O.	Reilly, Philip J.
Grayson, Charles E.	Rooney, Pierce A.
Lambert, Lewis	Smiley, Stanley
Martin, James	Steinberg, Stuart
Pope, Glenn A.	Terry, Daniel
SAN BENITO (2)	
SAN BERNARDINO (6)	
Gibson, Thomas	Hill, Harold M.
Halburg, Clarence T.	Judd, Richard
Hendrickson, M. A.	Krikes, Nicholas P.
Miano, Ben D. A.	Sterling, Allen F.
Sprague, Charles P.	Wake, Donald K.
Varden, Arthur	Wilson, Richard J.
SAN DIEGO (14)	
Brumbaugh, Simon C.	Cowell, William E.
Carpenter, Walter F.	Dill, Donald
Hippen, Robert L.	Ford, John R.
Hokr, William K.	Heard, Jerome L.
King, Ralph M.	Herrick, William C.
Levy, Edward I.	Kirtland, Howard B., Jr.
Messenger, Harold	Peabody, Homer D., Jr.
Peck, Sam	Peck, J. Haddon A., Jr.
Plumb, Robert T.	Pierangelo, Anthony J.
Rumsey, John M.	Reck, Lawrence E.
Tancredi, Chester	Tisdale, William
Telford, Joseph W.	Wells, John J.
Youel, Milo A.	
SAN FRANCISCO (20)	
Baer, Charlotte C.	Barrios, Xavier O.
Bender, William T.	Bryan, John R.
Biskind, Gerson R.	Cohn, Bradford
Bonfilio, Nicholas D.	Coleman, Arthur H.
Feldman, Sanford E.	Cook, Robert E.
Fullenlove, Tom M.	Cullen, Stuart C.
Gallagher, Donald M.	Erskine, John M.
Gibbons, Henry, III	Fleming, Ruth
Herrod, Chester E.	Hopp, Eugene S.
Herzog, George K., Jr.	Kelley, Edward T.
Hurwitz, Samuel	Musser, Don C.
Lebo, Charles P.	O'Gara, Louis A.
Pillsbury, Philip	Pevehouse, Byron C.
Rixford, Emmet L.	Robinson, Saul J.
Saunders, John B. deC. M.	Rosenberg, Alan J.
Schaffarzick, Ralph W.	Salomon, Maurice S.
Schaupp, John B.	Scholten, Paul
Sirbu, Abraham B.	Solari, Rafael A.
Wayburn, Edgar	Webb, Eugene M.
Williams, A. Justin	Wellington, C. J.

Delegates	*Alternate*
SAN JOAQUIN (4)	
Benn, James J.	Clark, Stanley A., Jr.
McNally, John	Evans, Wesley
Salter, Robert K.	Morozumi, John
Williams, George	Wass, Warren
SAN LUIS OBISPO (2)	
Chambers, James R.	Kolb, Karl P.
Fryer, Harry J., Jr.	Warren, L. H.
SAN MATEO (7)	
Fox, Norman C.	Ellis, Eldon E.
Hart, Ward L.	Hansen, James R.
Healy, Francis A.	Kohn, Martin M.
Hills, Oscar W.	Richanbach, Henry S.
Lindsey, Howard W.	Rossiter, Stanford B.
Novak, Frank J.	Storli, Edgar A.
Saidy, John T.	Thompson, William H.
SANTA BARBARA (4)	
Blanchard, John P.	Elam, Eldon
McNiece, Kenneth	Gebhart, William
Miles, Harold	Owens, Daniel E.
Ziemba, Joseph	Rutten, R. John
SANTA CLARA (13)	
Besson, Gerald	Althaus, Charles
Blanchard, Leland	Bonar, Samuel
Boice, Clyde	Brown, James L.
Davis, Burt L.	Burnett, Robert
Fox, Leon P.	Houck, George
Giansiracusa, Frank	Johnson, Allen
Kaufman, S. Fred	Manson, R. Morton
Liston, Edward	Nola, Vincent F.
McCort, James J.	Parker, Malcolm
Mitchell, Sidney	Rowles, Donald
O'Neill, Robert J.	Schade, Hugh
Scarborough, C. Gerald	Upton, Hubert M.
Skillicorn, Stanley A.	Zoglin, Stanton
SANTA CRUZ (2)	
DePuy, J. L.	Berman, Irwin B.
Mills, Richard G.	Nelson, Carl
SHASTA-TRINITY (2)	
Martin, George A.	Jantzen, Roland R.
Polka, Michael G.	Keye, John, Jr.
SISKIYOU (2)	
Geyman, John P.	Anderson, Robert
SOLANO (2)	
Gullock, Alvin H.	Garrett, Robert L.
Schmutz, M. A.	Olson, William J.
SONOMA (3)	
Barnett, Richard C.	Butler, Robert H.
Clary, David T.	Dunn, William J.
Craven, Wayne M.	Lones, Frank E.

Delegates	*Alternate*
STANISLAUS (3)	
Nelson, William	Bigelow, Wayne B.
New, David J.	Hatch, F. N.
Purvis, Robert	Pote, William W.
TEHAMA (2)	
Ingle, Gerald	Cooper, I. V.
Wood, O. T.	Merhoff, Hugh
TULARE (2)	
Goettle, James W.	Feldmayer, James E.
Lavers, George D.	Wulff, Verna
VENTURA (4)	
Hair, Charles M.	Mathews, Albert L.
Huff, W. Cloyce	Pallais, Armando
Moore, James W.	Sherrill, Glenn D.
Rulfo, Henry J.	Steniger, David H.
YOLO (2)	
Sobeck, Frederick J.	Loofbourow, J. C.
Wilson, B. Kent	Werblun, Merrill
YUBA-SUTTER-COLUSA (2)	
Boyer, Warren	Cusick, George
Wright, Bayard A.	Wallace, Robert N.

EX-OFFICIO SCIENTIFIC BOARD (18)

Belford, William W.	Halter, Bert L.
Bettman, Jerome W.	Kelly, Hobart M.
Blanchard, Leland B.	Stein, Justin J.
Brockman, Seymour J.	Wood, David A.
Clinco, Arthur A.	
Dillon, John B.	
Goebel, James L.	
Goerke, L. S.	
Grayson, Charles E.	
Jones, Ellis W.	
Kenney, Edmund L.	
Levan, Norman E.	
McCandless, Carl M.	
Petit, Donald W.	
Richards, Victor	
Rubin, David	
Russell, Keith P.	
Zaik, Edward J.	

EX-OFFICIO PAST PRESIDENTS (23)

Peers, Robert A. 1935	Charnock, Donald A. . . . 1956
Wilson, Harry H. 1940	MacDonald, Frank A. . . . 1957
Molony, William R., Sr. . . 1942	West, Francis E. 1958
Schaupp, Karl L., Sr. . . . 1943	Reynolds, T. Eric 1959
Cline, John W. 1947	Foster, Paul D. 1960
Askey, E. Vincent 1948	Bostick, Warren L. 1961
Kneeshaw, R. Stanley 1949	Wheeler, Omer W. 1962
Cass, Donald 1950	Sherman, Samuel R. 1963
MacLean, H. Gordon 1951	Doyle, James C. 1964
Green, John W. 1953	Teall, Ralph C. 1965
Morrison, Arlo A. 1954	MacLaggan, James C. . . . 1966
Shipman, Sidney J. 1955	

EX-OFFICIO HONORARY PAST PRESIDENT (1)

Murray, Dwight H.

House of Delegates • 1968 Annual Session

AGENDA

Room of the Dons — Peacock Court

Speaker.....William F. Quinn, Los Angeles
Vice-Speaker.....Joseph F. Boyle, Los Angeles
Secretary.....Helen B. Weyrauch, San Francisco

FIRST MEETING, Saturday, March 23, 1968
REGISTRATION — 3 p.m.
MEETING STARTS — 4 p.m. SHARP

1. Call to order.
2. Announcement of Reference Committees and Miscellaneous Announcements.
 (a) Committee on Credentials. (Delegates must register with the Committee.)
 (b) Reference Committee on the Reports of Ofcers, the Council, the Commissions and Standing and Special Committees. (Reference Committee No. 1.)
 (c) Reference Committee on Finance, to study and make recommendations to the House of Delegates on the budget, submitted by the Council and appropriate committees, and the amount of dues for the ensuing year. (Reference Committee No. 2.)
 (d) Reference Committee on Resolutions and New and Miscellaneous Business. (Reference Committee No. 3.)
 (e) Reference Committee (No. 3A) on Resolutions and New and Miscellaneous Business.
 (f) Reference Committee (No. 3B) on Resolutions and New and Miscellaneous Business.
 (g) Reference Committee on Amendments to the Constitution and Bylaws. (Reference Committee No. 4.)
 (h) Reference Committee on CPS Business.
3. Honored Guests.
 (a) Fifty-year Members.
 (b) Past Presidents.
 (c) Allied Health Groups.
4. Report of Committee on Credentials, and Organization of the House of Delegates—Roll Call.
5. Recognition of President of the Woman's Auxiliary to the CMA—Mrs. William R. Flood.
6. Address by President—John G. Morrison.
7. Report of the President—John G. Morrison.
8. Report of the President-Elect—Malcolm C. Todd.
9. Report of the Speaker and Vice-Speaker of the House of Delegates—William F. Quinn and Joseph F. Boyle.
10. Report of the Trustees of the California Medical Association—John G. Morrison.
11. Report of Physicians' Benevolence Fund, Inc.——John G. Morrison.
12. Report of the Secretary—Helen B. Weyrauch.
13. Report of the Editor—Malcolm S. M. Watts.
14. Report of the Executive Director — Robert L. Thomas.
15. Report of Legal Counsel—Peart, Hassard, Smith & Bonnington.
16. Report of the Committee for Emergency Action —John G. Morrison.
17. Report of the Council—Albert G. Miller, Chairman.
18. Report of CBS Board of Trustees—Richard L. Wilbur, Chairman, Board of Trustees.
19. Reports of Commissions.
 (a) Commission on Medical Services—Arthur F. Howard, Fresno.
 (b) Commission on Public Agencies—William F. Kaiser, Berkeley.
 (c) Commission on Community Health Services —James H. Yant, Sacramento.
 (d) Commission on Communications—Elmer F. Gooel, Beverly Hills.
 (e) Commission on Professional Welfare — George K. Herzog, Jr., San Francisco.
 (f) Judicial Commission—Francis E. West, San Diego.
 (g) Commission on Allied Health Professions and Services—Frank C. Melone, Ontario.
 (h) Commission on Hospital Affairs—James C. MacLaggan, San Diego.
 (i) Scientific Board—William P. Longmire, Jr., Los Angeles.
20. Reports of Other Committees.
 (a) Bureau of Research and Planning—Carl E. Anderson, Santa Rosa.
 (b) Role of Medicine in Society—Malcolm S. M. Watts, San Francisco.
 (c) Organization Review & Planning—Jean F. Crum, Downey.
 (d) Committee on Legislation—Dan O. Kilroy, Sacramento.
 (e) Finance Committee—Harold Kay, Oakland.
 (f) Medical Executives Conference — Eldon E. Geisert, Bakersfield.
 (g) Delegates to the AMA—Eugene F. Hoffman, Sr., Los Angeles.
21. Old and Unfinished Business.
22. New Business.

SECOND MEETING, Tuesday, March 26, 1968, at 3:00 p.m.

(To be recessed and reconvened at 9:00 a.m. Wednesday, March 27.)

ORDER OF BUSINESS

1. Call to order.
2. Supplemental report of Credentials Committee—Roll Call.
3. Introduction of President-Elect of Woman's Auxiliary—Mrs. Robert J. Douds.
4. Address by President-Elect—Malcolm C. Todd.
5. Secretary's announcement of Council's selection of time and place for the 1969 Annual Session.
6. Election of Officers:
 (a) President-Elect.
 (b) Speaker.
 (c) Vice-Speaker.
 (d) Councilors (three-year terms):
 (1) Second District—Frank C. Melone, Ontario (term expiring).
 Second District—Inyo, Mono, Riverside and San Bernardino Counties.
 (2) Fourth District—Office No. 1—Sam S. Woolington, Long Beach (term expiring).* (Three-year term.)
 (3) Fourth District—Office No. 4—Lewis T. Bullock, Los Angeles (term expiring).
 (4) Fourth District—Office No. 7—Wilbur G. Rogers, Glendale (term expiring).
 (5) Fourth District—Office No. 9—Robert L. Watson, Jr., Los Angeles (term expiring).* (Two-year term.)
 Fourth District—Los Angeles County.
 (6) Seventh District—Office No. 2—Albert G. Miller, San Mateo (term expiring).
 Seventh District—Monterey, San Benito, San Mateo, Santa Clara and Santa Cruz Counties.
 (7) Eighth District—Office No. 1—Albert G. Clark, San Francisco (term expiring).* (One-year term.)
 Eighth District—San Francisco County.
 (8) Eleventh District—James H. Yant, Sacramento.
 Eleventh District—Alpine, Butte, Colusa, El Dorado, Glenn, Lassen, Modoc, Nevada, Placer, Plumas, Sacramento, Shasta, Sierra, Siskiyou, Sutter, Tehama, Trinity, Yolo and Yuba Counties.
 (e) Delegates to the American Medical Association:
 (Delegates and Alternates to the American Medical Association are elected for terms of two calendar years. The Delegates and Alternates to be elected at this meeting will serve for two calendar years starting January 1, 1969, except as otherwise noted.)

 INCUMBENTS:
 (1) John G. Morrison, San Leandro (term expiring).
 (2) William F. Quinn, Los Angeles (term expiring).
 (3) Robert C. Combs, San Francisco (term expiring).
 (4) Homer C. Pheasant, Los Angeles (term expiring).
 (5) Alfred J. Murrieta, Los Angeles (term expiring).
 (6) Burt L. Davis, Palo Alto (term expiring).
 (7) Arlo A. Morrison, Ventura (term expiring).
 (8) James E. Feldmayer, Exeter (term expiring).
 (9) O. W. Wheeler, Riverside (term expiring).
 (10) Malcolm C. Todd, Long Beach (term expiring).
 (11) J. E. Vaughan, Bakersfield (term expiring).
 (12) Carl E. Anderson, Santa Rosa (term expiring).
 (f) Alternates to the American Medical Association:
 (Terms of all incumbents expiring. All offices for two year terms starting January 1, 1969, except as otherwise noted.)
 (1) Frederick Ackerman, Pleasant Hill (alternate to John G. Morrison).
 (2) Dudley M. Cobb, Los Angeles (alternate to William F. Quinn).
 (3) Emmett Rixford, San Francisco (alternate to Robert C. Combs).
 (4) James C. MacLaggan, San Diego (alternate to Homer C. Pheasant).
 (5) Harold Kay, Oakland (alternate to Alred J. Murrieta).
 (6) Leon P. Fox, San Jose (alternate to Burt L. Davis).
 (7) Henry Brown, San Mateo (alternate to Alro A. Morrison).
 (8) Charles Grayson, Sacramento (alternate to James E. Feldmayer).
 (9) Wilbur Bailey, Los Angeles (alternate to O. W. Wheeler).
 (10) Neil C. Hamel, Encino (alternate to Malcolm C. Todd).
 (11) Joseph P. O'Connor, Pasadena (alternate to J. E. Vaughan).
 (12) Jean F. Crum, Downey (alternate to Carl E. Anderson).

*Council Designees.

7. Election of California Blue Shield Trustees (three-year terms):
 Report of CMA Council as Nominating Committee.
 Incumbents, terms expiring:
 Richard F. Altman
 Burt L. Davis
 Donald R. Fitch
 Bert Halter
 Mr. Philip S. Magruder (ineligible for re-election)
8. Announcements by Secretary.
 Council's nominations of members of Commissions and Committees.
 (For approval by the House of Delegates.)
9. Reports of Reference Committees:
 (a) Reports of Reference Committee No. 1 on Reports of Officers, the Council, Commission and Standing and Special Committees.
 (b) Report of Reference Committee No. 2 on the Budget submitted by the Council and appropriate committees, and the dues for the ensuing year.
 (c) Report of Reference Committee No. 3 on Resolutions and New Miscellaneous Business.
 (d) Report of Reference Committee No. 3A on Resolutions and New and Miscellaneous Business.
 (e) Report of Reference Committee No. 3B on Resolutions and New and Miscellaneous Business.
 (f) Report of Reference Committee No. 4 on Amendments to the Constitution and Bylaws.
 (g) Report of Reference Committee on CPS Business.
10. Unfinished Business.
11. New Business.
12. Presentation of Officers:
 President—Presentation of Plaque to President John G. Morrison.
 President-Elect.
 Speaker.
 Vice-Speaker.
13. Approval of Minutes. (Committee to edit.)
14. Adjournment.

WILLIAM F. QUINN, *Speaker*
HELEN B. WEYRAUCH, *Secretary*

Constitutional Amendments

FOR ACTION IN 1968

One constitutional amendment was introduced in the 1967 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

This proposed amendment is shown here for the information of the membership. In addition, the proposed Constitutional amendment is required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

* * *

CONSTITUTIONAL AMENDMENT NO. 1-67

Woman's Auxiliary; Article I, Sec. 6

Introduced by: Council

Resolved: That a new Section 6 be added to Article I, as follows:

"Section 6.—Woman's Auxiliary to the California Medical Association.

"In addition to the organizational structure previously set forth in this Article, this Association may charter a Woman's Auxiliary to the California Medical Association, and components thereto, which shall be considered an integral part of the Association but which shall conduct its own organization and business separate and distinct from the Association and its Societies, subject to the following requirements:

"a. The name of the Auxiliary shall be 'Woman's Auxiliary to the California Medical Association,' (hereinafter referred to as Auxiliary);

"b. The purpose of the Auxiliary shall be to promote the science and art of medicine, the protection of public health and the betterment of the medical profession, and to promote similar interests of its component Auxiliaries;

"c. The Auxiliary shall be composed of the component Auxiliaries and their members;

"d. Component Auxiliaries shall include all women's auxiliaries to component Medical Societies of the California Medical Association heretofore or hereafter chartered by this Association;

"e. Charters to component Auxiliaries shall be granted and revoked by the Association as it may provide; provided that no charter issued by the Association, nor any action of the Association in issuing or revoking such charters, shall conflict with the purposes and principles of this Association as set forth in its Constitution and Bylaws."

ANNUAL REPORTS FOR 1967

REPORT OF THE

President

To the House of Delegates:

When I was installed as President of the California Medical Association last year, I predicted that the twelve months ahead would present medicine with many challenges and problems. This prognosis proved to be correct—beyond even my expectations.

Nowhere were problems more evident than in the Medi-Cal area. Was there truly a fiscal crisis? This depended not only upon whom one was talking to, but *when*. Were the emergency cuts by the Health and Welfare Agency legal? The same equivocal answer. In the midst of this general confusion regarding the Medi-Cal program, CMA tried to make every reasonable effort to cooperate with the Administration, pledging to continue to provide the best care possible under the emergency measures. At the same time, we strongly urged the Administration to restore as soon as possible those aspects of Assembly Bill 5 which CMA had originally supported when the legislation was passed—aspects which made it a medically sound piece of welfare legislation for those who truly need such assistance. These basic concepts are, in brief:

- free choice of physician and hospital by the patient.
- payment of reasonable fees to physicians and reimbursement of hospitals on the basis of reasonable costs.
- coverage for a broad spectrum of care including at least physicians' services, hospital and nursing home care, laboratory and x-ray services, dental services, prescribed drugs, and other medically necessary benefits.
- medical care financed under the prepayment concept (when possible) and fiscally administered through carriers of prepaid health care protection.

In November, 1967, we publicly raised questions regarding the alleged fiscal crisis, suggested ways to improve the Med-Cal program and reaffirmed our support of the basic concepts outlined above. We pledged our "fullest cooperation to the future development and implementation of a quality Medi-Cal program," and stated that "we cannot advise our Association, its members, the Legislature, or the public to support an inferior health care program." We have continued to pursue a *medically sound* Medi-Cal program—stating our convictions as forcefully as possible, to as many concerned persons as possible, as often and consistently as possible.

Although Medi-Cal captured the headlines in 1967, a variety of other subjects of vital importance to the health care of Californians demanded the time and attention of your officers. Distribution of health manpower within the state received both study and action during the past year. CMA continued its cooperative efforts with allied organizations through the recently formed Health Manpower Council. We also sponsored our own Conference on Distribution of Health Manpower in Rural California. Again, involvement of many disciplines was the keynote. Contributions from medical school faculty and students were of particular value. Specific recommendations from that conference are now being implemented.

During 1967 the status of California's mental health facilities was questioned by the public after criticism by a prominent foreign physician. CMA responded with an offer to conduct an independent survey of all state institutions for the mentally ill and retarded, similar to the survey we conducted in 1964. At this writing, this second survey has been completed and the results are being prepared for release.

Professional liability insurance was another subject of great concern during 1967. A comprehensive CMA survey on professional liability was conducted, and CMA and the California Hospital Association jointly sponsored a pilot workshop to study in depth some of the more catastrophic

malpractice problem areas. Specific changes in state legislation to improve the professional liability picture are actively being sought.

Our efforts in the field of government relations have extended to the national level. For example, in June, 1967, a team of seven physicians and four staff members representing CMA and California Blue Shield visited all forty of California's Congressional offices in Washington, D.C. This new venture was extremely successful in terms of opening lines of communication between the medical profession in California and its representatives in Washington.

During 1967 CMA intensified its efforts to involve more persons and organizations in the activities and interests of the Association. In October, we sponsored our first conference with medical specialty organizations — a significant step in strengthening relationships with these societies and improving CMA's position as the Association which represents and speaks for all California physicians.

Efforts have also been made to communicate more closely with component society leadership. Two regional meetings of component society presidents held in conjunction with meetings of the CMA Council provided an opportunity for informal discussion of the problems facing medicine in California and how both CMA and local societies can work together in approaching these problems in more effective ways. The constructive suggestions given by local leaders at these meetings have been invaluable to your officers and councilors.

In this brief written report, I have had a chance to touch on only a few of the multiple issues in which CMA has been involved during the past year. I look forward to presenting a more comprehensive oral report to the House of Delegates at the time of the Annual Meeting.

Respectfully submitted,
JOHN G. MORRISON, M.D., *President*

REPORT OF THE

President-Elect

To the President and the House of Delegates:

As I have traveled to various county medical societies in the northern part of the state during the past year, I have become increasingly impressed with the vigor and understanding with which physicians are approaching the problems and challenges currently facing medicine.

In particular, I have been gratified to learn of the active involvement of many local societies in the implementation of federal legislation pertaining to health — Public Law 89-239 (Regional Medical Programs) and Public Law 89-749 (Comprehensive Health Planning). As an appointed member of the Governor's recently formed State Health Planning Council, and chairman of the CMA Task Force on Public Law 89-749, I have had the opportunity to attempt to guide the implementation of this tremendously broad law so that it will enhance rather than detract from present methods of providing and delivering health care to Californians. I am pleased to know that so many local physicians share my concern in this area.

Many other vital subjects have demanded the time and attention of myself and others. The complexity and variety of the challenges faced by medicine—from Medi-Cal to malpractice insurance—have generated innumerable special meetings and conferences with state officials and others. In addition, I have attended many regular CMA committee and commission meetings at which your designated representatives have tried to come to grips with countless issues. I am deeply impressed with the astute insight and willing contribution of hours of study and deliberation evidenced by your representatives on these committees. The Association could not function without this involvement and participation. I urge all members of the House of Delegates to read the committee reports as published in the ANNUAL REPORTS BULLETIN to gain an impression of the tremendous scope of activities in which this Association is involved.

I look forward to supplementing these brief comments with a personal presentation to the House of Delegates.

Respectfully submitted,
MALCOLM C. TODD, M.D., *President-Elect*

REPORT OF THE

Council

To the President and the House of Delegates:

The Council of the California Medical Association is responsible for managing the affairs of the

organization; implementing the policies approved by the CMA House of Delegates at its annual meeting, and determining CMA policies between annual meetings of the House of Delegates.

The Council usually meets ten times in regular session between meetings of the House of Delegates; this year a special meeting was called in August to consider measures to be taken in light of the impending cuts in the Medi-Cal program.

Minutes of all Council meetings have been published in CALIFORNIA MEDICINE in the earliest possible issue after each meeting. Many details of Council considerations and actions are contained in these reports. Council highlights are published on the Monday immediately after each meeting in the weekly MEDICAL EXECUTIVES MEMO. Additional details also are available from the Association's office and staff. Each member should feel free to request any desired information.

The composition of the Council is geographical, numerically uniform and representative of all major fields of practice of California physicians.

Reports by all standing commissions and committees and by special committees appointed for specific purposes may be given at each Council meeting.

By inviting representatives of other health-oriented organizations, officials of state agencies concerned with public health and deans of medical schools in California to its regular meetings, the Council maintains constant contact and communication with them. During the past year, attendance and interest by these organizations in the meetings of the Council have indicated their desire to maintain and build the liaison that has been developed.

Ample opportunity is given to all members and guests to speak freely and in detail. Officers of county medical societies are invited to attend each Council meeting. County society executive secretaries attend regularly.

Councilor attendance at meetings is usually 100 per cent with an occasional absence for good cause.

This report will not go into detail on Council actions but will discuss briefly some of the major areas of interest and activities which have engaged the Council during the past year.

1. *Actions of the 1967 House of Delegates.* The Council supervised the implementation of all resolutions adopted by the 1967 House of Delegates. Copies of all resolutions adopted and a report on the actions will be mailed in advance of the 1968 House of Delegates meeting to all members of the House. Wherever feasible, the author of each resolution has been contacted and the actions on his resolution made known to him. Where resolutions have been introduced in the name of a delegation, the chairman of the delegation and/or the major county society within that delegation area has been informed and has been requested to notify the appropriate author.

2. *CMA Staff Organization and Structure.* In July, Mr. Robert L. Thomas was appointed Executive Director of the California Medical Association. Since his appointment, Mr. Thomas has undertaken reorganization of the staff structure of the CMA, forming seven Divisions. New staff members include Mr. John Pompelli, who is Director of the Division of Government Relations and Mr. Milton D. Krueger, who is Director of the Division of Professional and Public Relations.

In addition, the Council approved a specialty conference which was attended by representatives of the various specialty organizations in the state, to determine how they could better work with the CMA through their representatives.

The Council authorized two meetings for presidents of county medical associations, and postponed the County Society Officers Conference from January to September. It was felt that two regional meetings would give the rural presidents an opportunity to discuss their ideas and opinions, as well as to attend a regular meeting of the Council.

3. *Medi-Cal Program.* As it has since 1965, Medi-Cal and Medi-Cal amendments occupied a great deal of time of the CMA Council. Throughout the year the Council had stressed the importance of providing high quality medical care to Medi-Cal recipients. In the face of significant decreases in services that could be provided to Medi-Cal patients, CMA Council issued statements in August and October and again in November, calling for support of the CMA membership in providing high quality care and cooperating with the state administration as far as possible in keeping the costs of this program at a minimum.

A press conference was called in August, suggesting three possible solutions for the fiscal crisis:

(1) Items not medically required should be excluded.

(2) Selected controls could be placed on some medical procedures.

(3) The administration should implement suggestions made earlier by the CMA to place some control on nursing home admissions.

In September, Council reaffirmed its belief in "mainstream" care and asked for restoration of usual and customary fees and all necessary services. In November, the Council issued a 12-point policy statement calling for full restoration of services, tightening of administrative procedures, the use of deductible and co-insurance and the services of an independent actuary to determine the true fiscal situation.

In December, the Council asked the State to make clear to the residents of California that custodial care in nursing homes is not properly covered by Medi-Cal and is not a medical problem.

In addition, CMA Council reaffirmed its previous position that physicians in teaching/county hospitals should be paid for services under Medi-Cal on the same basis as is provided in the Medicare law.

Council has approved a resolution passed by the San Francisco Medical Society that called for increased participation in utilization review by physicians and for strict observance of usual, customary and reasonable fees by all physicians when billing Medi-Cal patients.

4. *Public Law 89-749.* Comprehensive health planning took on new and major meanings as the year went on. A Task Force on P.L. 89-749 was formed of ten members of the Council and was given the responsibility of keeping the Council informed of progress being made throughout the state in implementing this far-reaching new legislation.

The Council approved a grant from the federal government for a Western Conference on Comprehensive Health Planning which was sponsored by CMERF and held in November in Chandler, Arizona. This Conference, which was attended by more than 200 persons from 14 western states, provided an ideal forum for the exchange of experiences and projections of things to come.

5. *Mental Health Survey.* Once again, the quality of care in the state's mental institutions was questioned by people of the state, and CMA Council offered the services of the CMA to Governor Reagan in making a special survey of the 14 state hospitals. The survey was completed by mid-January and a report delivered to the Governor and legislative representatives.

6. *Osteopathy.* The osteopathy situation again was creating problems and the Council approved in July an informational program to remind Californians of why osteopathy and medicine were merged in the state. A three-pronged approach to the problem is planned.

(1) Question and answer brochure will be developed for public consumption.

(2) Medical school deans will cooperate in showing the public that manipulation is being taught in the regular medical school curricula.

(3) A comparative study is being made of medical and osteopathic schools to show the quality of education delivered in each.

7. *Drug Abuse.* The Council adopted a statement on drug abuse in August. The statement was hailed throughout the state as a long-awaited and necessary position to be taken by the medical community. The statement received wide publicity in newspapers and other public media throughout the state.

8. *Professional Liability Insurance.* The Council authorized a study on professional liability insurance to answer many questions that were arising throughout the state. The survey was mailed to almost 4,000 physicians in private practice and the results made available either in toto or in part to the membership through the Bureau of Research and Planning. In addition, the Council approved Senate Interim Committee testimony which suggested the following seven ways in which the malpractice law in California could be improved:

- The statute of limitations should be tightened to provide a specific commencement point, and to make the period of limitation definite.
- The present concepts of privileged communications should be extended to county medical review committees and should include information given in confidence to the State Board of Medical Examiners.
- The effect of the doctrine of *res ipsa loquitur* (the thing speaks for itself) should be limited to getting the case before the jury.
- A plaintiff should be required to file a nominal bond before filing suit to prevent needless actions.
- Reasonable limits for damages under personal injury awards should be set to insure that premium rates for this type of coverage will not become prohibitive.

- Insurance carriers should be permitted to make immediate advance payment to an injured party without admitting liability by so doing.
- Some boundaries should be set on the doctrine of "informed consent."

9. *Joint Projects with CHA.* CMA's relationship with California Hospital Association was strengthened when Bill Whelan, who formerly was Associate Executive Director of the CMA, was named new Executive Director of CHA. The two organizations are working cooperatively on many programs including health manpower recruiting, a system of joint data collection, and joint workshops on professional liability problems.

Actions taken by the Council after the preparation of this report will be submitted in a supplemental report at the 1968 meeting of the House of Delegates in San Francisco.

The Council is especially indebted to President John G. Morrison and President-Elect Malcolm C. Todd. Both have devoted an extraordinary amount of time, effort and talent representing the California Medical Association before any number of private and public bodies and working with our own committees and other organizations in this year of complex new government programs and problems of increasing scope. They have been unstinting in their services and to them we owe a debt of gratitude. The same applies to a number of Councilors, commission and committee members, CMA and AMA delegates and others who have given so freely of their time and talents in presenting the true picture of medical practice in California to so many interested listeners. Special thanks are also due our dedicated staff of loyal employees who must and do adjust to the demands of the moment. Without their devoted services the work of the Association could not be accomplished.

Respectfully submitted,

ALBERT G. MILLER, M.D., *Chairman*

REPORT OF THE *Executive Director*

To the President and the House of Delegates:

In this, my first annual report to the House of Delegates as Executive Director of CMA, I would like to supplement the traditional topics (building arrangements, financial status, membership) with some remarks on recent reorganization within the CMA staff.

Since I joined the CMA staff in 1951, I have been impressed with the flexibility and dedication with which staff members approach their job of carrying out the policy decisions established by this Association. However, events of the past few years have multiplied and magnified the increasingly complex issues in which the CMA is involved on nearly a daily basis. This trend promises to continue—at an accelerated rate. As a primary step in providing for the most efficient and effective coordination of staff efforts in this challenging environment, the staff has been reorganized along more formal lines. We now have completed a table of organization, defining areas of responsibility, accountability and authority. I believe it will carry the Association through a long growth period.

Seven basic Divisions encompassing all staff activities have been established. The directors of these seven Divisions form the core management group who are responsible for coordination and administrative implementation of your policies and programs. The complete table of staff organization is available on request. For the purposes of this report, I would like briefly to describe the seven Divisions and their areas of responsibilities.

Division of Government Relations. Responsible for:

- relationships with federal and state government bodies and their related health programs.
- coordination of committee programs which are in response to federal or state law or the programs administered or controlled by a state governmental agency, bureau or department.

Director: John Pompelli;
Assistant Director: Richard Lemos;
Administrative Assistant: Marge Heafey.

Division of Financial Affairs. Responsible for:

- development and maintenance of fiscal analyses and cost control systems for the Association and its related organizations.
- development and maintenance of the Association's annual budget.
- establishment of systems by which the Association can achieve its financial goals.

Director: Lytton Hetland.

Division of Community Affairs. Responsible for:

- liaison with community-oriented organizations, agencies and local government bodies which are concerned with or participate in health matters.
- coordination of committee programs which are aimed at community health and environmental problems.

Director: Jack Collins;
Assistant Director: Mike Goldman;
Administrative Assistant: Heather McFarlane.

Division of Socio-Economics and Research. Responsible for:

- activities of an economic or business nature, which affect or assist the individual physician in his practice.
- all basic developmental and applied research activities undertaken by the Association and its affiliated organizations.
- contacts with other groups and organizations concerned or active in the social and economic aspects of medical care and medical practice.

Director: Murray Klutch;
Assistant Director: Mike Jones.

Division of Scientific and Educational Activities. Responsible for:

- Annual Scientific Assembly and the other scientific and educational activities of the Association.
- all liaison with voluntary health-oriented organizations or teaching institutions within the health professions field.
- development and publication of scientific journals, articles, statements, and coordination of scientific meetings.
- all activities related to the general field of Health Education.

Director: Eugene Miller, M.D.;
Associate Director: Margaret Griffith.

Division of Professional and Public Relations. Responsible for:

- communication of CMA activities to both the Association membership and the general public.
- editorial and publication services for all Association publications except CALIFORNIA MEDICINE.

Director: Milton Krueger;
Assistant Director: Ed Collins;
Administrative Assistant: Helen Bratt.

Division of Administrative Services. Responsible for:

- development of internal systems and procedures and the CMA office services functions.
- all physical arrangements, management and direction of meetings, conferences and coordination of arrangements for the Annual Session.

On an interim basis, this Division will be under the direction of David Hicks. Jack Collins will serve as the coordinator of the arrangements for the 1968 Annual Session.

Assistant Director: David Hicks.
Administrative Assistant: Dorothy Dabney.

Office of the Executive Director. In carrying out my administrative responsibilities, I am assisted by three individuals:

Communications Assistant: Donna Redfern;
Administrative Assistants: Betty Schallenberger and Kay Cotner.

Several new names appear on the staff roster, filling vacant positions:

Mr. Milton Krueger, Director of Professional and Public Relations, joined the staff in December. He holds a bachelor's degree in business administration and a master's degree in journalism. Before joining our staff, he spent 15 years as Executive Secretary of the Medical Association of Georgia.

Mr. John Pompelli, Director of Government Relations, joined us in January. He was graduated with a degree in Industrial Relations. He has worked with organized medicine at the county, state and national levels: assistant executive secretary, Colorado State Medical Society (four years); executive secretary, Denver Medical Society (two years); and with the AMA Field Staff (four years) and as an AMA Legislative Advocate (two years).

Mr. Roger Miller, Research Analyst, Government Relations, holds a degree in Communications and Public Policy. Prior to joining the staff this year, Mr. Miller was Administrative Assistant to a California legislator. He has also served as Research Analyst for the State Assembly. He is responsible for researching and reporting fiscal implications of proposed state legislation and government programs, as well as the state budget. He works out of our Sacramento office.

It is impossible to single out any one individual on the staff as outstanding, but I do want to share with the members of the House of Delegates my pride in the accomplishments of the staff in the Sacramento office of the Association. Working with the staff of the Public Health League, these men and women have served the medical profession well.

Building Arrangements

CMA maintains its principal office at 693 Sutter Street, San Francisco, in a building owned by the trustees of the California Medical Association. Offices also are maintained in Los Angeles and Sacramento. The Sacramento office continues as a joint effort with the Public Health League. It serves as headquarters for the CMA Committee on Legislation and a portion of the Government Relations staff.

As your staff has grown in both number and effectiveness, space in all of our offices has become a real problem. Our efforts to adjust space have been dubbed "Operation Shoehorn."

Financial Status

(Financial Reports, pages 63-71)

The Association is operating on a sound financial basis. During the past five years, there has been a growth in net worth of $639,669 (exclusive of the net worth of the Audio-Digest Foundation of $242,500 as of 30 June 1967). The internal cost controls and administrative safeguards are effective even though we are constantly facing increases in the cost of doing business.

The handling of CMA finances runs into several millions of dollars and includes the management of the Association and its four subsidiary organizations:

Trustees of the California Medical Association;

Physicians' Benevolence Fund, Inc.;

Six Ninety Three Sutter Publications, Inc.;

California Medical Education and Research Foundation.

Annual financial reports of all these organizations appear on another page of this issue, in the form of Balance Sheets and Operating Statements for Fiscal Year Ending 30 June 1967. These figures are taken directly from the audited reports of John F. Forbes and Co., Certified Public Accountants.

CMA's Annual Report for Fiscal Year ending 30 June 1967, reflects an increase of Assets over Liabilities in the amount of $123,498. As a result of this increase, the total Excess of Assets over Liabilities was increased from $33,712 as of 30 June 1966, to $157,210 as of 30 June 1967.

Trustees of the California Medical Association.

The Statement of Income and Expense of the Trustees of the California Medical Association, which is a holding company for accumulative net assets of the Association, shows a net gain of $7,959 for fiscal year ending 30 June 1967, as compared with a net gain of $26,457 for the preceding fiscal year. This reduction in net gain was brought about primarily by the cost of an architectural study, increased taxes, janitorial and other maintenance costs, and alterations to the building. Nevertheless the net worth of the Trustees stood at $1,349,129 as of 30 June 1967.

California Medicine. CALIFORNIA MEDICINE reflects an excess of *expenses* over *income* for the fiscal year ending 30 June 1967, in the amount of $7,066, as against an excess of *expenses* over *income* for the previous fiscal year of $31,192. The substantial reduction of this deficit was due primarily to increased advertising income.

While no attempt has been made to present a detailed financial analysis of California Medical Association, the Trustees or other subsidiaries, I have attempted to highlight those items which may be of interest to the membership. We invite your close examination of the audited statements. Questions will show your interest.

Membership

On 1 September 1967, the date on which an official membership count is taken for purposes of representation in the House of Delegates, the Association showed 22,396 active members, a gain of 579 members over the total recorded a year earlier. Membership gains were reported by 30 component

societies while eight showed a membership loss and two no change. The active membership of all component societies as of the first of September 1967 and the corresponding date a year earlier is shown in the following table:

Active Membership in the CMA by Component Societies

	Sept. 1 1966	*Sept. 1 1967*
Alameda-Contra Costa	1,796	1,859
Butte-Glenn	116	126
Forty-First	137	140
Fresno	388	411
Humboldt-Del Norte	95	95
Imperial	47	48
Inyo-Mono	17	19
Kern	263	254
Kings	41	45
Lassen-Plumas-Modoc-Sierra	23	22
Los Angeles	8,755	8,856
Marin	237	239
Mendocino-Lake	52	51
Merced	77	76
Monterey	200	209
Napa	88	93
Orange	1,156	1,236
Placer-Nevada	95	96
Riverside	343	357
Sacramento	625	663
San Benito	7	7
San Bernardino	479	502
San Diego	1,194	1,255
San Francisco	1,856	1,876
San Joaquin	279	288
San Luis Obispo	92	95
San Mateo	597	605
Santa Barbara	335	344
Santa Clara	1,191	1,242
Santa Cruz	134	133
Shasta-Trinity	79	87
Siskiyou	22	24
Solano	89	94
Sonoma	214	221
Stanislaus	179	191
Tehama	18	17
Tulare	127	122
Ventura	237	254
Yolo	66	76
Yuba-Sutter-Colusa	71	68
TOTAL	21,817	22,396

Conclusion

During the coming year, staff efforts will be directed toward measurable accomplishments in implementing policies and in achieving the objectives of the Council and House of Delegates.

A report on staff activity would be incomplete without a word of appreciation for the outstanding cooperation and support given to our efforts by the county society executive secretaries. Many thanks to these men and women. As we enter a new period of activity for California Medicine, we will continue our close teamwork to keep CMA in the national leadership role it has occupied for so long and to increase the profession's effectiveness and stature within the state.

Respectfully submitted,
ROBERT L. THOMAS, *Executive Director*

REPORT OF THE

AMA Delegation

To the President and the House of Delegates:

During the past year, the CMA Delegation to the AMA House of Delegates continued actively to represent the physicians and the public of California and of the country in the major deliberations of the highest policy-making body of the medical profession. The extent of its activity can be gauged by the large number of special reports and resolutions presented at each of the two conventions held during the year. During the Annual Convention in Atlantic City, the delegation was faced with some fifty reports and 116 resolutions; there were 40 reports and 57 resolutions at the Clinical Convention in Houston. All of these reports and resolutions require study and involvement when reference committees are held and the House convenes, thereby necessitating their assignment to various members of the CMA Delegation, as well as discussion and decision on the part of the entire delegation with regard to the policy to be advocated when various issues come up for vote.

In addition, of course, the delegation introduces resolutions referred to it by the CMA House of Delegates or by the Council or others, which it may deem necessary to sponsor. For example, at the Annual Convention, the delegation introduced 19 resolutions of which 15 were adopted by the AMA House, two referred for further consideration, two served as the basis for other policy decisions and only two were not adopted. At the recent Clinical Convention, the delegation introduced five resolutions of which one was adopted and the remaining four referred to the Board of Trustees either for implementation or information and study or transmittal to several Councils of the AMA for further action. The one which was adopted and which required a considerable amount of work was that which will bring the 1973 Clinical Convention to Anaheim instead of to Las Vegas.

The delegation is efficiently organized into a number of committees, each of which has a specific responsibility for carrying out particular functions

during and in between meetings. In addition, each member of the delegation is assigned specific resolutions and reports which go to the various reference committees after the delegation has discussed them and decided upon the policy it wishes to pursue on behalf of CMA.

The delegation was most pleased to see its efforts rewarded in the unanimous election of Dwight L. Wilbur as president-elect and of Burt L. Davis to the Board of Trustees. Doctor Wilbur's inauguration as president at the 1968 Annual Convention to be held in San Francisco will be a highlight to which all of us are looking forward, and the delegation sincerely hopes that the scientific program as well as other activities will attract the largest number of physicians of any meeting held in recent years.

With the election of Doctor Davis to the Board of Trustees, I was elected chairman of the delegation and Samuel R. Sherman, vice-chairman. Together with the chairmen of our various committees: Doctors Robert Combs (Resolutions), Al Miller (Hospitality), Arlo Morrison (Rules), Emmet Rixford (Alternates), Ralph Teall (Candidates), and Jack Vaughan (Ace Deuce), and with the support of all the delegates and alternates we hope to be able to continue to carry out the wishes and desires of the members of the California Medical Association to the best of our ability.

Respectfully submitted,

EUGENE F. HOFFMAN, SR., M.D., *Chairman*

REPORT OF THE

California Blue Shield

To the President and the House of Delegates:

Enrolled Membership

As of 30 November 1967, the enrolled membership of California Blue Shield programs was 1,292,902 persons, representing a net gain of 145,067 persons over the total enrolled on 30 November 1966, which was 1,147,835 persons.

Of the total membership on 30 November 1967, 44.4 per cent (573,645 persons) were enrolled under Usual Fee programs. These figures do not include an enrolled group of approximately 17,000 persons which will convert to a Usual Fee program on 1 January 1968.

Physician Membership

Physician membership on 31 December 1967 was 17,420. During the year a statewide check of physician members against the Master Provider File employed for the processing of Medi-Cal claims indicated that 172 physicians had left active practice in California, although still carried in our records as members. On closer investigation it was found that death, retirement, military service and change of residence accounted for the discrepancy. Our records were adjusted accordingly.

Financial

Standard Blue Shield Programs

Based on actual figures for the first eleven months of the year, plus estimated figures for December 1967, operating income for the year was approximately $80,000,000. Disbursements under the Standard Programs will be approximately $69,000,000. Figures similarly developed in 1966 were respectively,

Operating Income	$73,500,000
Disbursements	64,000,000

reflecting substantial growth in 1967.

The Stabilization Reserve Fund will be about $19,360,000, figured on an eleven-month actual figure plus an estimated figure for December 1967, an increase of about $890,000 over the final, adjusted figure for the year 1966.

Government-Financed Programs

Federal Medicare. Since 1 July 1966, California Blue Shield had processed and paid 2,664,812 Medicare Part B claims. As of 2 January 1968, the amount of $123,367,338 had been disbursed in claims payments.

The changes brought about by HR 12080, which was signed into law by the President on 2 January, have been analyzed and the required adjustments to accommodate them have been made within Blue Shield's operations.

Medi-Cal (California Medical Assistance Program). California Blue Shield has administered all the benefits of the Medi-Cal program except those for hospitalization and care in related facilities, since the inception of the program in March 1966. Between that date and 2 January 1968, the organization has paid 27,129,764 Medi-Cal claims in the amount of $337,883,113. The Medi-Cal program is achieving an increasing stability. The most frustrating problems are being solved.

CHAMPUS (Civilian Health and Medical Program, U.S.). Based upon actual figures for eleven months and a conservative estimate of December 1967 experience, CHAMPUS claims paid during 1967 will be about $8,500,000.

We have had some serious problems with the administration of the CHAMPUS program during the year. Primarily, these were caused by the computerization of CHAMPUS claims handling, the necessity to program some 500,000 procedural fee profiles into the computer system, and hire and train inexperienced personnel. These steps have now been taken, but in the process of taking them the claim payment cycle was disrupted and claims backlogs developed. We are hopeful that these can be eliminated within the next few months.

California Physicians' Insurance Corporation. CPIC, the indemnity insurance company subsidiary of California Blue Shield, attained an estimated gross annualized premium income in 1967 of $9,540,000.

In force, group life insurance almost doubled during the year, rising from a 1966 year-end level of $34,512,500 to an estimated $67,500,000 at year-end 1967.

Assets increased from $2,472,000 at the end of 1966 to an estimated $3,000,000 at the end of 1967. These figures confirm the promise of orderly growth evidenced by CPIC in past years.

General

The greatly accelerated growth of usual and customary fee programs is indicative of management interest in responding to the wishes of the House of Delegates over several years. Despite the magnitude of our involvement with Government-financed programs, the Board and Management of California Blue Shield have never overlooked the fact that the organization's original, and continuing, reason for being was to provide effective prepaid medical care programs for groups and individuals in the private sector. It is the intent of the Board of Trustees and Management to continue to offer flexible, effective programs in this sector at the lowest cost compatible with prudent management.

Respectfully submitted,
RICHARD S. WILBUR, M.D.
Chairman of the Board

REPORT OF THE

Physicians' Benevolence Fund, Inc.

To the House of Delegates:

Physicians' Benevolence Fund, Inc. was established to respond to requests for temporary assistance from physicians or their families throughout the state of California. The Operating Committee periodically meets and reviews both policies and activities of the Fund. Requests for assistance are reviewed and are passed on by the Committee based on the immediate need and are not designed to constitute a retirement income program. Appeals are investigated on the local level and periodic reports on recipients are reviewed. All cases of real need are tactfully and sympathetically handled. The recipients are for the most part widows and children of physicians.

Income for the Fund is received from an allocation of $1 out of annual dues paid by each active member of the Association. In addition, contributions have been received from the Woman's Auxiliary. Interest earned has been derived from U.S. Treasury Bonds and Bills and temporary loans to affiliated organizations.

The Fund received $31,788 during the fiscal year ending 30 June 1967, and made expenditures of $21,706. The excess of income over expenses in the amount of $10,082 went directly into reserves. Total assets now stand at $193,340.

The Operating Committee consists of Clyde L. Boice, M.D., Chairman; and Doctors Elizabeth Mason Hohl, Dudley M. Cobb, Jr., Alexander Frazier, Don Z. Musser, and George Wolfe. There are no paid employees of the Fund and the only Operating Expenses of the Fund are the costs of an annual audit and the cost of the meeting of the Operating Committee.

An expression of appreciation is due the Woman's Auxiliary for continued support in maintaining this benevolent assistance program for the temporary relief of distressed physicians, their widows, and children.

Respectfully submitted,
JOHN G. MORRISON, M.D., *President*

REPORT OF

Certified Public Accountants

CALIFORNIA MEDICAL ASSOCIATION:

We have examined the balance sheets or statements of assets at June 30, 1967, and the related statements of income and expenses or expenditures for the year then ended of California Medical Association (a nonprofit association) and the following affiliated companies:

Trustees of the California Medical Association;
Physicians' Benevolence Fund, Inc.;
California Medical Education and Research Foundation; and
Six Ninety Three Sutter Publications, Inc.

Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial position of each of the foregoing organizations at June 30, 1967, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

The accompanying supplemental schedules referred to in the aforementioned financial statements, although not considered necessary for a fair presentation of the financial condition and the results of operations of the respective organizations, have been subjected to the audit procedures applied in the examinations of the financial statements, and in our opinion are fairly presented.

JOHN F. FORBES & COMPANY

San Francisco, California
August 10, 1967

CALIFORNIA MEDICAL ASSOCIATION
(A Nonprofit Association)

Balance Sheet
June 30, 1967 and 1966 and Comparison

	JUNE 30 1967	JUNE 30 1966	Increase (Decrease)
ASSETS			
CASH	$ 71,474	$230,907	$ *(159,433)*
CERTIFICATE OF DEPOSIT—CROCKER-CITIZENS NATIONAL BANK	1,000,000		1,000,000
UNITED STATES TREASURY BILLS, AT COST		593,275	*(593,275)*
ACCOUNTS RECEIVABLE, NET	102,630	56,942	45,688
ACCRUED INTEREST	9,409	4,780	4,629
NOTE RECEIVABLE:			
Central California Blood Bank	71,000	74,000	*(3,000)*
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1)	18,204	14,855	3,349
Insurance	4,398	3,021	1,377
Deposits	1,834	1,484	350
Other	1,372	1,665	*(293)*
Total prepaid expenses and other assets	25,808	21,025	4,783
FURNITURE AND FIXTURES (Note 2)	23,125	1	23,124
	$1,303,446	$980,930	$ 322,516
LIABILITIES			
ACCOUNTS PAYABLE:			
American Medical Education Foundation	$ 108,228	$207,985	$ *(99,757)*
Other	138,995	70,634	68,361
Total accounts payable	247,223	278,619	*(31,396)*
DEFERRED INCOME:			
Dues and subscriptions applicable to the succeeding fiscal year	894,783	667,272	227,511
Other	4,230	1,327	2,903
Total deferred income	899,013	668,599	230,414
EXCESS OF ASSETS OVER LIABILITIES (Note 3)	157,210	33,712	123,498
	$1,303,446	$980,930	$ 322,516

See notes to financial statements.

Statement of Income and Expenses
Years Ended June 30, 1967 and 1966 and Comparison

	YEAR ENDED JUNE 30 1967	YEAR ENDED JUNE 30 1966	Increase (Decrease)	Per Cent of Change
INCOME:				
Membership dues, less portion allocated to CALIFORNIA MEDICINE subscriptions	$1,669,828	$1,479,506	$190,322	12.9
Booth rentals at annual session	40,935	40,515	420	1.0
Postgraduate fees	15,363	16,560	*(1,197)*	*(7.2)*
Fee for collection of American Medical Association dues	14,997	9,494	5,503	58.0
Interest earned	20,483	11,462	9,021	78.7
Other	1,220	1,006	214	21.3
	1,762,826	1,558,543	204,283	13.1
EXPENSES:				
Operational (Schedule 1)	416,683	349,941	66,742	19.1
Other than operational (Schedule 2)	1,251,688	1,203,831	47,857	4.0
	1,668,371	1,553,772	114,599	7.4
EXCESS OF INCOME OVER EXPENSES FOR THE YEAR	94,455	4,771	89,684	1,879.8
OTHER CREDITS AND (CHARGES):				
Reduction of allowanee for possible loss on Central California Blood Bank note		84,500	*(84,500)*	
Refund of pension premium on past service, net	29,043	20,460	8,583	42.0
Payment under loan guaranty agreement		*(46,000)*	46,000	
	29,043	58,960	*(29,917)*	*(50.7)*
EXCESS OF ASSETS OVER LIABILITIES (LIABILITIES OVER ASSETS):				
Increase for the year	123,498	63,731	59,767	93.8
At beginning of year	33,712	*(30,019)*	63,731	212.3
	$ 157,210	$ 33,712	$123,498	366.3

See notes to financial statements.

NOTE:

1. EMPLOYEE PENSION PLANS

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has completed the funding of a Past Service Pension Plan for certain full-time employees. The amount on deposit with the administrator at June 30, 1967, aggregated $79,853. These funds are to be used to purchase annuity contracts as eligible employees retire. Neither the amount on deposit nor any liability for pensions is carried on the books of the Association or included in the accompanying balance sheet.

2. FURNITURE AND FIXTURES

Assets acquired during the year ended June 30, 1967 are stated at cost less accumulated depreciation of $2,533. Acquisitions prior to July 1, 1966 are carried at a nominal amount of $1. At May 13, 1966, the firm of Marshall and Stevens, appraisers, estimated that the sound value of assets then owned was $104,415.

3. SUBSIDIARIES

The Trustees of the California Medical Association, a wholly-owned incorporated subsidiary of the California Medical Association, holds in trust a large portion of the assets utilized by the Association and related organizations. The combined net worth of the two organizations is summarized as follows:

Entity	JUNE 30 1967	JUNE 30 1966	Increase (Decrease)
California Medical Association	$ 157,210	$ 33,712	$123,498
Trustees of the California Medical Association	1,349,129	1,341,170	7,959
	$1,506,339	$1,374,882	$131,457

The combined net worth at June 30, 1967 shown in the summary above does not include the following items:

California Medical Association:	
Excess of the appraised value of furniture and fixtures acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value (Note 2)	$ 93,973
Audio-Digest Foundation, a wholly-owned subsidiary; net worth at June 30, 1967 as shown by the Foundation's audited balance sheet	242,500
	336,473
Trustees of the California Medical Association—Excess of net worth over Trustees' investment in their wholly-owned subsidiary, Pacific Magnetic Tape Co., based on that company's unaudited balance sheet at June 27, 1967	21,798
	$358,271

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION
(A Nonprofit Corporation)

Balance Sheet
June 30, 1967 and 1966 and Comparison

	JUNE 30 1967	JUNE 30 1966	Increase (Decrease)
ASSETS			
CASH	$ 24,423	$ 3,311	$ 21,112
MARKETABLE SECURITIES, AT COST OR MATURITY VALUE (Note 2):			
United States Treasury bonds (market value $1,001,072)	1,119,152	1,119,152	
United States Treasury bill		19,779	*(19,779)*
Total marketable securities	1,119,152	1,138,931	*(19,779)*
NOTE AND ACCOUNT RECEIVABLE	2,850	2,400	450
ACCRUED INTEREST ON SECURITIES	2,119	2,307	*(188)*
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES, AT COST:			
Pacific Magnetic Tape Equipment Co. (Note 1)	9,000	9,000	
Six Ninety Three Sutter Publications, Inc.	1,000	1,000	
Total investments in wholly-owned subsidiaries	10,000	10,000	
PROPERTIES, AT COST (Note 4):			
Land	180,217	87,400	92,817
Buildings and improvements	378,383	295,938	82,445
Furniture and fixtures	5,198		5,198
	563,798	383,338	180,460
Less accumulated depreciation	83,685	69,817	13,868
Properties, net	480,113	313,521	166,592
EQUIPMENT, AT NOMINAL VALUE	1	1	
CASH SURRENDER VALUE OF LIFE INSURANCE	40,838	35,708	5,130
DEPOSIT IN ESCROW		10,000	*(10,000)*
PREPAID INSURANCE	3,800	2,525	1,275
REAL ESTATE TAXES APPLICABLE TO SUBSEQUENT YEAR (contra)	19,000	11,500	7,500
	$1,702,296	$1,530,204	$172,092
LIABILITIES			
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
California Medical Association	$ 17	$ 800	$ *(783)*
Interest and accrued expenses	2,408	199	2,209
Real estate taxes (contra)	19,000	11,500	7,500
Total accounts payable and accrued expenses	21,425	12,499	8,926
NOTES PAYABLE:			
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of $2,506, including interest, to March 1, 1973) (Note 4)	48,541	56,295	*(7,754)*
Crocker-Citizens National Bank—Unsecured	150,000		150,000
Total notes payable	198,541	56,295	142,246
TRUST FUNDS (Note 2)	115,789	106,740	9,049
DEFERRED COMPENSATION PAYABLE	16,500	13,500	3,000
DEFERRED INCOME	912		912
EXCESS OF ASSETS OVER LIABILITIES (Note 3):			
Contributed	883,193	883,193	
Excess of income over expenses (Exhibit D)	465,936	457,977	7,959
	1,349,129	1,341,170	7,959
	$1,702,296	$1,530,204	$172,092

See notes to financial statements.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Statement of Income and Expenses Years Ended June 30, 1967 and 1966

	YEAR ENDED JUNE 30 1967	1966
INCOME:		
Excess of rental income over property expenses (property expenses over rental income) (Schedule 4)	$ (7,910)	$ 12,370
Interest on United States Treasury bonds and bills	29,278	28,324
Dividend—Pacific Magnetic Tape Equipment Co.	900	900
Miscellaneous	52	34
	22,320	41,628
EXPENSES (OTHER THAN PROPERTY)—FEES AND INSURANCE	4,308	2,339
	18,012	39,289
OTHER CHARGES:		
Net premium on life and retirement insurance policy	4,053	4,176
Provision for retirement or other benefit of an employee of an affiliated organization	3,000	3,000
Provision for deferred compensation	3,000	3,000
Loss on sale of securities		2,656
	10,053	12,832
EXCESS OF INCOME OVER EXPENSES:		
Current year	7,959	26,457
Beginning of year	457,977	431,520
End of year	$465,936	$457,977

See notes to financial statements.

Notes to Financial Statements June 30, 1967

NOTE:

1. WHOLLY-OWNED SUBSIDIARY

The Trustees of the California Medical Association owns all of the outstanding stock of the Pacific Magnetic Tape Equipment Co., which was formed for the purpose of merchandising magnetic tape equipment as an adjunct to the activities of the Audio-Digest Foundation, a wholly-owned subsidiary of the California Medical Association. An unaudited balance sheet of the Pacific Magnetic Tape Equipment Co. at June 27, 1967, shows a net worth of $30,798 at that date.

2. MR. AND MRS. BEN H. READ RETIREMENT

The portion of the Trust Funds applicable to the retirement or similar benefit to Mr. and Mrs. Beu H. Read, amounting to $57,000 at June 30, 1967, has not been segregated from other assets of the corporation as provided by the bylaws, as such funds are presently invested in United States Treasury securities of indivisible denominations.

3. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

	JUNE 30 1967	1966	Increase
Entity			
California Medical Association	$ 157,210	$ 33,712	$123,498
Trustees of the California Medical Association	1,349,129	1,341,170	7,959
Combined net worth	$1,506,339	$1,374,882	$131,457

The combined net worth at June 30, 1967 shown in the summary above does not include the following items:

California Medical Association:	
Excess of the appraised value of furniture and fixtures acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value	$ 93,973
Audio-Digest Foundation, a wholly-owned subsidiary; net worth at June 30, 1967 as shown by the Foundation's audited balance sheet	242,500
	336,473
Trustees of the California Medical Association—Excess of net worth over Trustees' investment in their wholly-owned subsidiary, Pacific Magnetic Tape Co., based on that company's unaudited balance sheet at June 27, 1967	21,798
	$358,271

4. PROPERTIES

On October 10, 1966, the Trustees of the California Medical Association purchased the land and building located at 679 Sutter Street. The properties are summarized as follows:

	693 Sutter Street	679 Sutter Street	Total
Land	$ 87,400	$ 92,817	$180,217
Buildings and improvements	300,494	77,889	378,383
Furniture and fixtures	5,198		5,198
	393,092	170,706	563,798
Less accumulated depreciation	80,927	2,758	83,685
	$312,165	$167,948	$480,113

The property located at 693 Sutter Street, San Francisco, is subject to a deed of trust to The Connecticut Mutual Life Insurance Company in the amount of $48,541.

PHYSICIANS' BENEVOLENCE FUND, INC.
(A Nonprofit Corporation)

Statement of Assets
June 30, 1967

ASSETS		
CASH—CROCKER-CITIZENS NATIONAL BANK		$ 6,381
INVESTMENTS (market value $129,500):		
U.S. Treasury 2½% bonds at maturity values:		
Maturity date, December 15, 1969	$10,000	
Maturity date, December 15, 1972	34,000	
U.S. Treasury bills, at cost	89,172	133,172
NOTE RECEIVABLE WITH DEED OF TRUST AS COLLATERAL—LOS ANGELES COUNTY PHYSICIANS' AID ASSOCIATION (original amount, $50,000, maturing in quarterly installments of $1,000 plus interest at 2½% per annum)		26,000
ACCOUNTS RECEIVABLE		27,787
		$193,340
SOURCE OF ASSETS		
CONTRIBUTED AT ORGANIZATION		$ 92,132
EXCESS OF INCOME OVER EXPENDITURES		101,208
		$193,340

Statement of Income and Expenditures
Year Ended
June 30, 1967

INCOME:		
Contributions:		
California Medical Association (see note)	$22,008	
The Woman's Auxiliary of the California Medical Association	3,902	$ 25,910
Interest earned:		
U.S. Treasury bonds and bills	3,779	
Loans	2,099	5,878
		31,788
EXPENDITURES:		
Payments to beneficiaries:		
Los Angeles County Physicians' Aid Association	11,400	
Others	9,550	
	20,950	
Other	756	21,706
EXCESS OF INCOME OVER EXPENDITURES:		
Current year		10,082
Beginning of year		91,126
End of year		$101,208

NOTE: The constitution of the California Medical Association, Article IV, Section 6, provides: "At least $1 out of the annual dues paid by each active member of the Association shall be allocated to the Physicians' Benevolence Fund, Inc., a corporation, and shall be used for the purposes as set forth in that corporation's Articles and Bylaws."

CALIFORNIA MEDICAL EDUCATION AND RESEARCH FOUNDATION
(A Nonprofit Corporation)

Balance Sheet June 30, 1967

ASSETS		
CASH IN BANK		$22,132
ACCOUNTS RECEIVABLE:		
California Committee on Regional Medical Programs	$35,052	
Other	6,422	41,474
UNITED STATES TREASURY BILLS, AT COST		24,763
		$88,369
LIABILITIES AND FUND BALANCES		
ACCOUNTS PAYABLE:		
California Medical Association	$21,783	
Other (see note)	4,295	$26,078
FUND BALANCES:		
Audio-Digest Foundation grant	25,000	
California Committee on Regional Medical Programs	24,478	
General fund	12,813	62,291
		$88,369

See note to financial statements.

Statement of income, Expenditures and Fund Balances Year Ended June 30, 1967

	Total	Audio-Digest Foundation	U.S. Department of Health, Education, and Welfare (see note)	California Committee on Regional Medical Programs	General Fund
INCOME:					
Grants and restricted contributions	$70,052	$25,000	$10,000	$35,052	
Interest	877				$ 877
	70,929	25,000	10,000	35,052	877
EXPENDITURES:					
Contributions—California College of Medicine	27,500	27,500			
Services:					
Administrative	10,503		4,523	5,980	
Other	2,163		451	1,712	
Supplies and printing	1,897		674	1,055	168
Keypunch processing	109			109	
Mailing and postage	393			366	27
Telephone and telegraph	10			3	7
Travel and meeting	540			15	525
Charge to cover payroll taxes and employee benefits	1,248		489	759	
Professional fees	600				600
Other	977		151	575	251
	45,940	27,500	6,288	10,574	1,578
EXCESS OF INCOME OVER EXPENDITURES (EXPENDITURES OVER INCOME)	24,989	*(2,500)*	3,712	24,478	*(701)*
FUND BALANCE, JUNE 30, 1966	41,597	27,500	583		13,514
UNUSED FUNDS DUE GRANTOR TRANSFERRED TO ACCOUNTS PAYABLE	*(4,295)*		*(4,295)*		
FUND BALANCE, JUNE 30, 1967	$62,291	$25,000		$24,478	$12,813

See notes to financial statements.

Note to Financial Statements June 30, 1967

NOTE: COMPLETION OF STUDY

The Foundation received a community health project grant in the amount of $34,899 from the United States Department of Health, Education, and Welfare. The project funded by this grant was completed during the year at a cost of $30,604. The balance of the unexpended fund amounting to $4,295 will be returned to the grantor.

SIX NINETY THREE SUTTER PUBLICATIONS, INC.

Balance Sheet
June 30, 1967

ASSETS		
CASH		$ 5,981
ACCOUNTS RECEIVABLE:		
California Medical Association	$11,122	
Other	1,812	12,934
INVENTORY, AT COST		11,566
DEPOSIT AND PREPAID EXPENSES		292
		$30,773

LIABILITIES AND STOCKHOLDER'S EQUITY		
LIABILITIES:		
Accounts payable	$ 653	
Federal income tax payable	2,902	
Total liabilities		$ 3,555
STOCKHOLDER'S EQUITY:		
Capital stock (authorized, 2,500 shares of $10.00 par value each; issued and outstanding, 100 shares) (see note)	1,000	
Retained earnings	26,218	
Total stockholder's equity		27,218
		$30,773

NOTE: The Trustees of the California Medical Association is the sole stockholder of this Corporation.

Statement of Income and Retained Earnings
Year Ended
June 30, 1967

NET SALES			$58,840
COST OF SALES			36,935
GROSS PROFIT			21,905
EXPENSES:			
Office:			
Services	$2,400		
Rent	300		
Supplies	1,835		
Fees	450		
Other	233	$5,218	
Shipping:			
Services	301		
Postage, freight, and express, net	1,546	1,847	
Personal property taxes		409	
State franchise and sales tax		1,239	8,713
INCOME BEFORE FEDERAL INCOME TAX			13,192
FEDERAL INCOME TAX			2,902
NET INCOME			10,290
RETAINED EARNINGS, JUNE 30, 1966			15,928
RETAINED EARNINGS, JUNE 30, 1967			$26,218

Expenses other than Operational Years Ended June 30, 1967 and 1966 and Comparison

	YEAR ENDED JUNE 30 1967	1966	Increase (Decrease)	Per Cent of Change
SCIENTIFIC, EDUCATIONAL, AND COMMUNICATIONS:				
Medical services	$ 53,249	$ 24,493	$ 28,756	117.4
Public agencies	34,273	35,009	(736)	(2.1)
Community health services	66,086	68,750	(2,664)	(3.9)
Professional welfare	18,466	19,654	(1,188)	(6.0)
Hospital affairs	30,886	40,211	(9,325)	(23.2)
Bureau on communications	249,391	172,403	76,988	44.7
Special project	4,761	33,435	(28,674)	(85.8)
Bureau of research and planning	83,643	90,527	(6,884)	(7.6)
Library (socio-economic)	13,612	10,754	2,858	26.6
Allied health professions and services	18,529	17,511	1,018	5.8
Scientific board:				
Commission and miscellaneous committees	57,641	51,612	6,029	11.7
Medical education	35,838	42,848	(7,010)	(16.4)
Cancer committees	6,839	6,156	683	11.1
Other committees	127,727	83,915	43,812	52.2
	800,941	697,278	103,663	14.9
CONTRIBUTIONS:				
Physicians' Benevolence Fund, Inc.	22,008	21,524	484	2.2
Nurse recruitment		3,000	(3,000)	
American Medical Education Foundation	158,000	206,000	(48,000)	(23.3)
Medical libraries	5,000	5,000		
	185,008	235,524	(50,516)	(21.4)
PHYSICIANS' SERVICES AND PROGRAMS:				
Meeting expenses:				
Annual session	50,490	53,515	(3,025)	(5.7)
American Medical Association	49,138	62,627	(13,489)	(21.5)
Component Society officers	10,761	10,606	155	1.5
Student—American Medical Association	3,977	1,122	2,855	254.5
Council	10,432	11,349	(917)	(8.1)
Medical Society executives	7,898	7,400	498	6.7
Travel expenses:				
Officers	37,655	32,107	5,548	17.3
Council	39,777	36,324	3,453	9.5
Other	23,373		23,373	
Physicians' Placement Service	14,081	16,730	(2,649)	(15.8)
CALIFORNIA MEDICINE, net (Schedule 3)	7,066	31,192	(24,126)	(77.3)
Women's Auxiliary	11,091	8,057	3,034	37.7
	265,739	271,029	(5,290)	(2.0)
	$1,251,688	$1,203,831	$ 47,857	4.0

Operational Expenses Years Ended June 30, 1967 and 1966 and Comparison

	YEAR ENDED JUNE 30 1967	1966	Increase (Decrease)	Per Cent of Change
Rent	$ 19,140	$ 12,672	$ 6,468	51.0
Telephone and telegraph	25,377	15,486	9,891	63.9
Postage	7,591	5,878	1,713	29.1
Equipment purchases and maintenance and depreciation	3,971	7,219	(3,248)	(45.0)
Office supplies and expense	29,212	17,131	12,081	70.5
Office services	659	12,955	(12,296)	(94.9)
Salaries (see note below):				
Administrative	49,281	47,988	1,293	2.7
Clerical	87,270	61,080	26,190	42.9
Los Angeles office		10,652	(10,652)	
Taxes	32,693	23,698	8,995	38.0
Insurance	7,989	4,224	3,765	89.1
Professional fees and expense	47,811	42,155	5,656	13.4
Automation	1,140		1,140	
Travel expenses—administrative and staff	20,071	12,068	8,003	66.3
Memberships and subscriptions	3,679	5,061	(1,382)	(27.3)
Retirement and employee benefits	76,531	69,695	6,836	9.8
Miscellaneous	4,268	1,979	2,289	115.7
	$416,683	$349,941	$ 66,742	19.1

NOTE: The total payroll for years ended June 30 was $622,828 for 1967 and $528,946 for 1966, of which $486,277 and $381,644, respectively, are included in other expense classifications or were charged to other organizations.

CALIFORNIA MEDICAL ASSOCIATION

Income and Expenses of "California Medicine" Years Ended June 30, 1967 and 1966 and Comparison

	YEAR ENDED JUNE 30		Increase (Decrease)	Per Cent of Change
	1967	1966		
INCOME:				
Advertising	$231,060	$174,904	$56,156	32.1
Subscriptions:				
Allocated from dues	67,553	66,489	1,064	1.6
Nonmembers	3,163	3,020	143	4.7
Reprints	10,365	6,691	3,674	54.9
	312,141	251,104	61,037	24.3
EXPENSES:				
Printing	214,719	180,028	34,691	19.3
Illustrations	3,955	2,843	1,112	39.1
Advertising sales expense	15,844	21,000	*(5,156)*	*(24.6)*
Cash discounts	3,953	3,033	920	30.3
Addressing	2,628	1,986	642	32.3
Postage and mailing	11,742	11,084	658	5.9
Reprints	8,397	4,585	3,812	83.1
Salaries	42,886	44,276	*(1,390)*	*(3.1)*
Editorial assistance	5,700	4,025	1,675	41.6
Rent	4,108	3,516	592	16.8
Telephone and telegraph	1,649	3,475	*(1,826)*	*(52.5)*
Office supplies and sundry	3,626	2,445	1,181	48.3
	319,207	282,296	36,911	13.1
(EXCESS) OF EXPENSES OVER INCOME	$ *(7,066)*	$ *(31,192)*	$24,126	77.3

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Rental Income and Property Expenses Year Ended June 30, 1967

	693 Sutter Building	679 Sutter Building	Total
INCOME FROM RENTALS:			
California Medical Association	$60,540		$60,540
Other	13,567	$14,005	27,572
	74,107	14,005	88,112
EXPENSES:			
Taxes	11,693	4,036	15,729
Utilities	5,949	1,010	6,959
Janitorial service and maintenance	15,960	182	16,142
Repairs—Plumbing and electric	5,664	2,455	8,119
Alterations	11,614	1,317	12,931
Insurance	1,223	1,067	2,290
Interest	2,243	4,491	6,734
Elevator inspection and service	1,543		1,543
Supplies	1,086	167	1,253
Architect's fees	8,540		8,540
Other operating expenses	878	1,036	1,914
Depreciation	11,110	2,758	13,868
	77,503	18,519	96,022
(EXCESS) OF PROPERTY EXPENSES OVER RENTAL INCOME	$ *(3,396)*	$ *(4,514)*	$ *(7,910)*

application for HOTEL ACCOMMODATIONS

NINETY-SEVENTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 23-27, 1968

FAIRMONT AND MARK HOPKINS HOTELS, SAN FRANCISCO

House of Delegates Opening Session, Mark Hopkins, Saturday evening, March 23;
Scientific Sessions, Fairmont Hotel, begin Sunday morning, March 24.

1. Fill in the form below **completely** for room accommodations at the CMA's 1968 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, Fox Plaza—Suite 260, San Francisco, California 94102 by *March 1, 1968.*

HOTEL ROOM RATES*

	Single	Double and Twin	Suites
FAIRMONT — Atop Nob Hill	$18-34	$23-39	$45-114
MARK HOPKINS — Atop Nob Hill	18-29	23-34	48- 90
HUNTINGTON 1075 California	None	21-35	55- 95
ST. FRANCIS Powell and Geary	16-31	20-36	45-110
SIR FRANCIS DRAKE Powell and Sutter	15-22	19-26	70
HANDLERY INN 260 O'Farrell	20-26	24-30	None
CHANCELLOR HOTEL 433 Powell	None	13-15	None
PLAZA HOTEL Post and Stockton	None	14-17	None

*Rates subject to change

Send to: California Medical Association—*Housing Bureau*
Fox Plaza, Suite 260, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1968 Annual Session in San Francisco, March 23-27. House of Delegates Opening Session, Saturday, March 23, at the Mark Hopkins; Scientific Programs begin Sunday morning, March 24, at the Fairmont.

Single Bedroom $ Twin-Bedded $ Double Bed $

Small Suite $ Large Suite $ Other $

First Choice Hotel Second Third

Arrival (date) Hour a.m. p.m. Departure (date) Hour a.m. p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names and addresses of each person in a double or twin-bedded room, and names and addresses of all other persons for whom you are requesting reservations.

—PLEASE PRINT OR TYPE—

Your Name: Officer? Delegate? Alternate? Speaker?

Address: County

City and State Zip

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KEY TO ABBREVIATIONS USED

(BRP)—Bureau of Research and Planning; (CMA)—California Medical Association; (CR)—Case Report; (Ed.)—Editorial; (I)—Information; (LE)—Letter to Editor; (MP)—Medical Progress; (MSC)—Medical Staff Conference; (N/N)—News and Notes; (Or.)—Original Article; (PE)—Page End; (PHR)—Public Health Report.

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